

## TITLE PAGE

**Protocol Title:** A single centre, 2-period, randomized, open-label Phase 1 study to assess the relative bioavailability of a mesylate salt capsule of GSK3640254 compared to a hydrochloride salt capsule in healthy participants

**Protocol Number:** 208131 (QCL118221)

**Short Title:** A study to compare the relative bioavailability of two different formulations of GSK3640254

**Compound Number:** GSK3640254

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## 1. SYNOPSIS

**Protocol Title:** A single centre, 2-period, randomized, open-label Phase 1 study to assess the relative bioavailability of a mesylate salt capsule of GSK3640254 compared to a bis-hydrochloride salt capsule in healthy participants

**Short Title:** A study to compare the relative bioavailability of two different formulations of GSK3640254

**Rationale:** A First Time in Human (FTIH) study is in progress and has used the bis-hydrochloride salt immediate release capsule formulation of GSK3640254 administered following a moderate calorie and fat meal. However, the bis-hydrochloride salt formulation is not suitable for long term clinical development as it is susceptible to humidity. A mesylate salt capsule formulation of GSK3640254 has been generated for later phase development and commercialization. The aim of this relative bioavailability study is to compare the exposure of the mesylate salt capsule formulation of GSK3640254 (mentioned as GSK3640254 Mesylate Salt Capsule in regimens) with that of the bis-hydrochloride salt capsule formulation (mentioned as GSK3640254 Capsule in regimens) administered following a moderate calorie and fat meal.

### Objectives and Endpoints:

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> <li>To evaluate the pharmacokinetic (PK) profiles of GSK3640254 following administration of the mesylate salt capsule relative to that of the bis-hydrochloride salt capsule (reference) in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>GSK3640254 area under the curve from time zero to infinity (<math>AUC_{(0-\infty)}</math>), <math>AUC_{(0-tlast)}</math>, maximum observed concentration (<math>C_{max}</math>), Time to <math>C_{max}</math> (<math>T_{max}</math>), Concentration at 24 hours post-dose (<math>C_{24h}</math>), relative bioavailability (<math>F_{rel}</math>) based on AUC and <math>C_{max}</math></li> </ul>
Secondary	
<ul style="list-style-type: none"> <li>To provide additional information of the safety and tolerability of single doses of GSK3640254 in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers</li> </ul>

### Overall Design:

This is a Phase 1 study and will be conducted at a single centre. This study will include 2 treatment periods, during which each of the open-label treatments will be administered to each of the 2 treatment groups. It is planned to enroll 14 healthy participants.

**Number of Participants:**

Fourteen participants will be enrolled such that sufficient data will be available for at least 12 evaluable participants. An evaluable participant is a participant who has received both Regimens A and B, and has safety and PK data up to 72 hours post-dose.

Up to 7 replacement participants may be enrolled. The maximum number of participants that may be dosed is 21.

**Treatment Groups and Duration:**

Participants will receive a single oral dose of each study treatment (Regimens A and B) during each of the 2 inpatient periods, in a sequence of administration to be assigned via the randomization: AB or BA.

- Treatment Group AB: Regimen A is administered in Period 1, Regimen B is administered in Period 2.
- Treatment Group BA: Regimen B is administered in Period 1, Regimen A is administered in Period 2.

**Regimens:**

- Regimen A: An oral dose of 200 mg as 2 x 100 mg GSK3640254 Capsule, 100 mg (reference) following a moderate fat meal.
- Regimen B: An oral dose of 200 mg as 2 x 100 mg GSK3640254 Mesylate Salt Capsule, 100 mg (test) following a moderate fat meal.

Participants will receive the formulations in the morning after a moderate-fat breakfast (approximately 600 calories with approximately 30% of the calories from fat).

Each participant will be enrolled in the study for approximately 7 weeks, dependent on screening and washout duration between periods. Participation will include a screening evaluation within 28 days of first study treatment administration and 2 separate inpatient periods. Participants will be admitted to the clinic in the morning of the day before dosing (i.e. Day -1) for Periods 1 and 2, and in the evening of Day -1 for Period 2. Each inpatient period will consist of 4 days (Period 1, morning admission on Day -1) or 3 days (Period 2, evening admission on Day -1) and 3 nights followed by a return visit 72 hours post-dose.

There will be a minimum washout of 7 days between each dose of study treatment.

A follow-up visit will occur 7 to 10 days after the last dose of study treatment.

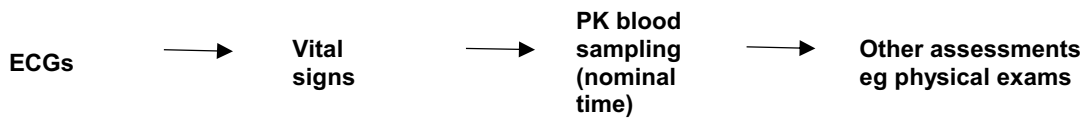
## 2. SCHEDULE OF ACTIVITIES (SOA)

The schedules of activities are presented in [Table 1](#). The time points for the PK blood sample collection, and ECG and vital sign assessments are presented in [Table 2](#).

The competent authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

The order of assessments will be:



Electrocardiograms will be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, e.g. physical examinations etc, will be performed within the required time windows. All safety assessments will be timed and performed relative to the start of dosing.

**Table 1 Schedule of Activities**

Procedure	Screening (up to 28 days before Day 1)	Treatment Periods 1 and 2 Day					Follow-up (7 to 10 days post last dose) or Early Discontinuation	Notes
		-1	1	2	3	4		
Outpatient visit	X					X	X	
Inpatient stay		X <sup>1</sup>	X	X	X <sup>2</sup>			1. Admission in the morning 2. Furlough from unit after assessments
Informed consent	X							
Inclusion and exclusion criteria	X	X <sup>3</sup>						3. Recheck clinical status at admission of Period 1
Demography	X							
Full physical examination including height and weight <sup>4</sup>	X							4. See Section 9.4.1 for systems to be examined
Columbia Suicide Severity Rating Scale (CSSRS)	X							
Brief physical examination			X <sup>5</sup>		X <sup>5</sup>		X	5. Pre-dose and 48 h post-dose See Section 9.4.1 for systems to be examined
Medical history (includes substance usage) <sup>6</sup>	X							6. Substances: Drugs, alcohol, tobacco and caffeine
Urine pregnancy test <sup>7</sup>	X	X					X	7. All female participants
Follicle stimulating hormone (FSH) <sup>8</sup>	X							8. As needed in women to confirm postmenopausal status
HIV, Hepatitis B and C screening	X							
Urine drug screen	X	X						



Procedure	Screening (up to 28 days before Day 1)	Treatment Periods 1 and 2 Day					Follow-up (7 to 10 days post last dose) or Early Discontinuation	Notes
		-1	1	2	3	4		
Alcohol breath test	X	X						
Carbon monoxide breath test	X	X						
Laboratory assessments (haematology, clinical chemistry and urinalysis)	X	X <sup>9</sup>			X <sup>9</sup>		X	9. 48 h post-dose Allowable windows in Section 9.4.4
12-lead ECG	X	X	X <sup>10</sup>	X <sup>10</sup>		X <sup>10</sup>	X	10. Time points in Table 2 Allowable windows in Section 9.4.3
Vital signs	X	X	X <sup>11</sup>	X <sup>11</sup>		X <sup>11</sup>	X	11. Time points in Table 2 Allowable windows in Section 9.4.2
Randomization			X <sup>12</sup>					12. Pre-dose Period 1 only
Study treatment			X					
AE review		X	←=====→				X	
SAE review	X	X	←=====→				X	
Concomitant medication review		X	←=====→				X	
PK blood sample collection <sup>13</sup>			←=====→					13. Time points in Table 2

**Table 2      Pharmacokinetic Blood Sampling Collection, ECG and Vital Sign Times**

	Treatment Periods 1 and 2															
Time (h)	Pre-dose	0	0.5	1	1.5	2	3	4	5	6	8	12	24	36	48	72
Dosing		X														
PK Sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG (repeat allowed)	X					X		X		X			X			X
Single set of Vital signs	X					X		X		X			X			X

### 3. INTRODUCTION

GSK3640254 is a next-generation HIV-1 Maturation Inhibitor (MI); this novel class of anti-human immunodeficiency virus (HIV)-1 medicines prevents the maturation of HIV-1 virions by binding near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly.

#### 3.1. Study Rationale

A First Time in Human (FTIH) study is in progress and has used the bis-hydrochloride salt immediate release capsule formulation of GSK3640254 administered following a moderate calorie and fat meal. However, the bis-hydrochloride salt formulation is not suitable for long term clinical development as it is susceptible to humidity. A mesylate salt capsule formulation of GSK3640254 has been identified for later phase development and commercialization. The aim of this relative bioavailability study is to compare the exposure of the mesylate salt capsule formulation of GSK3640254 with that of the bis-hydrochloride salt capsule formulation administered following a moderate calorie and fat meal.

#### 3.2. Background

Current therapy for HIV-infected individuals consists of a combination of approved antiretroviral (ARV) agents. More than twenty medicines are currently approved for HIV-1 infection, either as single agents, fixed-dose combinations or single-tablet regimens, the latter two containing 2 to 4 approved agents. Given the challenges inherent with the lifetime dosing of daily medications, there remains a need for new ARV agents that combine an optimal safety, tolerability and efficacy profile with a convenient dosing schedule. Significant toxicities have been described with each ARV agent in current use, and data continue to accumulate on the long-term clinical consequences of chronic ARV therapy [[Centers for Disease Control and Prevention](#), 2015; [Claessens](#), 2003; [Collins](#), 2006; [The DAD Study Group](#), 2007]. New ARV agents that offer an improved tolerability and safety profile are needed.

Despite the availability of different classes of ARV agents providing a variety of treatment options, treatment failure continues to occur as a result of high transmitted drug resistance, drug-associated toxicity and tolerability problems, and poor adherence to medication regimens. Although prevalence rates of drug resistance are falling in Western Europe, ~80% of HIV-infected patients who have received ARV therapy have resistance to at least one class of ARV [[De Luca](#), 2013]. Additionally, the prevalence of transmitted resistance to at least one ARV is ~10-17% in resource-rich regions, such as Europe [[WHO](#), 2012]. Unfortunately, resistance mutations selected by one ARV agent often confer resistance to multiple drugs in the same class, significantly limiting future therapeutic options. Later regimens often lack the convenience and tolerability of firstline drugs, which in turn exacerbates non-adherence. Thus, there is a continuing need for new classes of ARV drugs capable of providing potent, durable antiviral activity to a broad population of HIV-infected patients, with no cross-resistance to current agents, a relatively high barrier to the development of resistance on its own, and activity across diverse HIV-1 subtypes.

GSK3640254 is a next-generation HIV-1 Maturation Inhibitor (MI); this novel class of anti-HIV-1 medicines prevents the maturation of HIV-1 virions by binding near a key structural element within the Gag polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton HIV capsid protein p24 and spacer peptide 1. Blockage at this step results in the release of immature non-infectious virus particles. GSK3640254 has excellent potency and a broad pangenotypic spectrum in vitro. Laboratory studies confirm that GSK3640254 is an MI with a mechanism of action distinct from current ARVs, suggesting little if any risk of cross-resistance to current therapeutic agents.

As of 4 April 2018, the First Time in Human (FTIH) study is ongoing. It includes: 1) a single ascending dose (SAD) portion with doses of 1 mg to 700 mg (completed) and 2) a 14-day multiple ascending dose (MAD) portion (ongoing with 50 mg and 100 mg QD cohorts completed). The pharmacokinetics of GSK3640254 administered as a single dose following a moderate calorie/fat breakfast is characterized by a slow absorption with maximum concentration observed on average 3 to 4 hours after dosing. GSK3640254 is also slowly eliminated with an average half-life around 23 hours. C<sub>max</sub> and AUC tended to increase in a dose proportional manner from 1 mg to 400 mg with a less than dose proportional increase from 400 mg to 700 mg.

To support future toxicology studies to be conducted with the mesylate salt, single dose PK studies were conducted in male rats (doses of 10, 30 and 100 mg/kg) and male dogs (0.2, 1 and 5 mg/kg) with the mesylate salt. PK data were compared back to other PK studies conducted with the bis-hydrochloride salt. While the mesylate salt provided similar exposure as the bis-hydrochloride salt in dogs, the mesylate salt provided approximately a 75% increase in C<sub>max</sub> and AUC at the dose of 10 mg/kg with a smaller improvement of around 30% at the dose of 100 mg/kg in rats.

A detailed description of the chemistry, and the nonclinical pharmacology, pharmacokinetic and toxicology studies of GSK3640254 is provided in the Investigator's Brochure [GlaxoSmithKline Document Number [2016N294821\\_00](#)].

### **3.3. Benefit/Risk Assessment**

GSK3640254 is currently being studied in a Phase 1 SAD/MAD clinical trial in healthy participants to evaluate the safety, tolerability, and PK. The SAD portion of the study evaluating single doses ranging from 1 to 700 mg has been completed with preliminary data showing no major clinical safety or tolerability finding.

Until additional clinical safety information for GSK3640254 is available, precautions will be taken that are based on non-clinical safety assessment of GSK3640254 and reported clinical experiences of a previous, structurally similar maturation inhibitor (GSK3532795), in healthy and HIV-1 infected participants. Specifically, this previous maturation inhibitor (GSK3532795) was not progressed beyond Phase 2b clinical trials because of Grade 1-2 gastrointestinal intolerability (diarrhoea, abdominal pain) and treatment emergent resistance to study medications. In addition, two serious adverse events (SAEs; acute psychosis and suicidal/homicidal ideation) led to the early

termination of a Phase 1 Thorough QT (TQT) study in healthy participants at supratherapeutic doses.

Nonclinical findings with GSK3640254 have indicated the following potential risks for the clinical program: gastrointestinal (GI) intolerability/microscopic GI changes, cardiac conduction abnormalities (prolonged QT interval), hepatic injury (single cell necrosis), and renal changes (eosinophilic intracytoplasmatic inclusion bodies).

Until further preclinical studies on the effects of GSK3640254 on the reproductive system are available, it will be assumed that GSK3640254 has the potential to impair male and female fertility.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3640254 may be found in the Investigator's Brochure.

ViiV Healthcare has assessed this study for any risks that may be posed to participants taking part. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMA) guidance on strategies to identify and mitigate risks for FTIH clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07).

### 3.3.1. Risk Assessment

Potential risks of the IP (GSK3640254) are detailed below

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Investigational Product (IP) GSK3640254</b>		
GI intolerability/toxicity	<p><b><u>Non-clinical data:</u></b>            In a 14-day dose-range-finding study in rats, a non-tolerated dose of 300 mg/kg/day produced GI clinical signs and microscopic changes in the stomach and small intestine that were not seen at lower doses. These included minimal ulceration in the glandular stomach, minimal to moderate enterocyte vacuolation (lipid) in the duodenum, and minimal epithelial hyperplasia in the jejunum.            At tolerated doses, GI clinical signs occurred in rats (unformed faeces) at 100 mg/kg/day and dogs (sporadic vomiting and unformed, liquid or mucoid faeces) at <math>\geq 1</math> mg/kg/day.            At tolerated doses, reversible dose-responsive microscopic changes were observed in the stomachs of rats and dogs.</p>	<p><b><u>Participant selection:</u></b></p> <ul style="list-style-type: none"> <li>Participants with a clinically significant history of or current GI disorders will not be eligible to participate in this study</li> </ul> <p><b><u>Participant monitoring:</u></b></p> <ul style="list-style-type: none"> <li>Participants will be monitored for GI-related AEs</li> </ul>
Cardiac conduction abnormalities (prolonged QT interval)	<p><b><u>Non-clinical data:</u></b>            GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents with moderate potency. ECG changes attributed to GSK3640254 in telemeterized dogs at doses of 12.5 and 17</p>	<p><b><u>Participant selection:</u></b></p> <ul style="list-style-type: none"> <li>Participants with a history of or current cardiovascular disorders will not be eligible to participate in this study</li> <li>Participants with a QT interval corrected for heart rate according to Fridericia's formula</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>mg/kg consisted of increased rate-corrected QT interval from 3.5 to 6 hours post-dose (~ 9 msec) and during the overnight period (~ 6 msec). These QT effects were primarily limited to one dog given 17 mg/kg (<math>\leq 20</math> msec increase), with a plasma concentration of 7.96 <math>\mu\text{g/mL}</math> 8 hours after dosing.</p> <p>The no observed adverse effect level (NOAEL) in the study was 12.5 mg/kg, which produced similar systemic exposures (8.79 <math>\mu\text{g/mL}</math> 5 hours after dose).</p> <p>There were no GSK3640254-related effects on ECG parameters evaluated in the definitive general toxicity study in conscious restrained dogs given multiple doses of up to 25 mg/kg/day for 4 weeks.</p>	<p>(QTcF) <math>&gt; 450</math> msec at screening will not be eligible for this study</p> <p><b><u>Participant monitoring:</u></b></p> <ul style="list-style-type: none"> <li>• Participants will be monitored for cardiac-related AEs</li> <li>• ECGs will be monitored throughout the study</li> </ul>
Neurologic/psychiatric safety	<p><b><u>Clinical data:</u></b></p> <p>Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. From a neurologic and psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies, mild Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship was seen for</p>	<p><b><u>Participant selection:</u></b></p> <ul style="list-style-type: none"> <li>• Participants with a history of psychiatric disease requiring pharmacologic treatment in the last 5 years, any history of suicidal ideation (ever) or any clinically significant psychiatric history per investigator judgement will be excluded from the study</li> <li>• Protocol exclusion criterion based assessment using the CSSRS):</li> <li>• Participants will undergo physical exams and continuous evaluation for adverse events during their participation in the trial.</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>select neurologic and psychiatric AEs (based on TQT and P2b studies)</p> <p><b><u>Non-Clinical Data</u></b></p> <p>CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration</p>	

**Potential risks of study procedures are detailed below**

Study Procedures		
Cannulation	During cannulation more than one attempt may be needed to insert the cannula in a vein of a participant and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.	<ul style="list-style-type: none"> <li>• A vein assessment will be conducted at screening to ensure only volunteers with veins suitable for multiple venepuncture and cannulation are enrolled.</li> <li>• Cannulation and venepuncture will only be performed by staff who are trained in these procedures</li> </ul>
Electrocardiograms	Electrocardiogram stickers on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove.	<ul style="list-style-type: none"> <li>• Participants will be closely monitored to ensure any local irritation does not persist.</li> <li>• 2.5% hydrocortisone cream will be included in the list of permitted medication to relieve irritation from ECG leads.</li> </ul>



### 3.3.2. Benefit Assessment

There is no intended direct health benefit to the participants in this study.

### 3.3.3. Overall Benefit:Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the emerging clinical profile of GSK3640254 in the FTIH study, and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable.

## 4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b> <ul style="list-style-type: none"> <li>To evaluate the PK profiles of GSK3640254 following administration of the mesylate salt capsule relative to that of the bis-hydrochloride salt capsule (reference) in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>GSK3640254 area under the curve from time zero to infinity (<math>AUC_{(0-\infty)}</math>), <math>AUC_{(0-t_{last})}</math>, maximum observed concentration (<math>C_{max}</math>), Time to <math>C_{max}</math> (<math>T_{max}</math>), Concentration at 24 hours post-dose (<math>C_{24h}</math>), relative bioavailability (<math>F_{rel}</math>) based on AUC and <math>C_{max}</math></li> </ul>
<b>Secondary</b> <ul style="list-style-type: none"> <li>To provide additional information of the safety and tolerability of single doses of GSK3640254 in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>AEs, clinical laboratory values, vital signs, ECGs, and/or other safety biomarkers</li> </ul>

## 5. STUDY DESIGN

### 5.1. Overall Design

This is a single centre, 2-period, randomized, open-label Phase 1 study. It is planned to enroll 14 healthy participants. It is planned to study 2 regimens (A and B) during 2 periods (1 and 2).

The following regimens will be administered during each period in the study:

- Regimen A: An oral dose of 200 mg as 2 x GSK3640254 Capsule, 100 mg (reference) following a moderate fat meal.
- Regimen B: An oral dose of 200 mg as 2 x GSK3640254 Mesylate Salt Capsule, 100 mg (test) following a moderate fat meal.

Each participant will receive each of the regimens (Regimens A and B) in a sequence during Period 1 and Period 2 as determined by the randomization:

- Randomized to AB: Regimen A administered in Period 1, followed by Regimen B in Period 2
- Randomized to BA: Regimen B administered in Period 1, followed by Regimen A in Period 2

Participants will receive a single oral dose of study treatment during each inpatient period. Participants will receive the formulations in the morning after a moderate-fat breakfast (approximately 600 calories with approximately 30% of the calories from fat).

#### Study Outline:

**Period 1:** Participants will be admitted to the clinical unit on the morning of the day before study treatment administration (Day -1) for Period 1. Participants will receive a single oral dose of the assigned study treatment regimen on Day 1 and will remain on site until 48 hours post-dose, and then return to the clinical unit for a 72 hours PK sample, vital signs and ECGs.

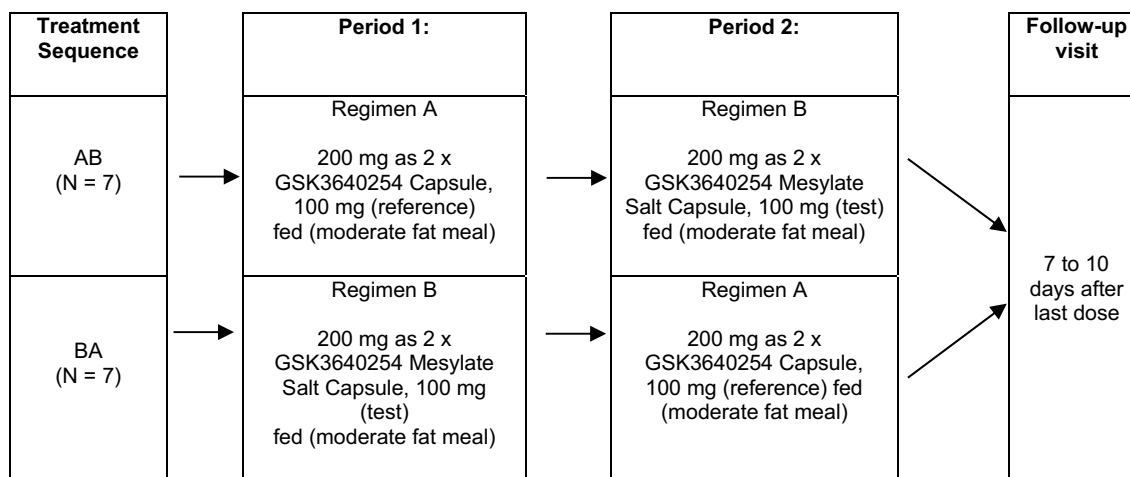
There will be a minimum washout of 7 days between each dose of study treatment.

**Period 2:** Participants will be admitted to the clinical unit on the morning of the day before study treatment administration (Day -1) for Period 2. Participants will receive a single oral dose of the assigned study treatment regimen on Day 1 and will remain on site until 48 hours post-dose, and then return to the clinical unit for a 72 hours PK sample, vital signs and ECGs.

**Follow up:** A Follow-up visit will be conducted 7 to 10 days after the last dose of study treatment.

The estimated maximum duration of the study from screening until follow-up for each participant is approximately 7 weeks.

**Figure 1 Study Design**



## **5.2. Number of Participants**

Fourteen participants will be enrolled such that sufficient data will be available for at least 12 evaluable participants. An evaluable participant is a participant who has received both Regimens A and B, and has safety and PK data up to 72 hours post-dose.

Up to 7 replacement participants may be enrolled. The maximum number of participants that may be dosed is 21.

Participants withdrawn by the investigator due to a moderate AE at least possibly related to study treatment will not be replaced. If participants prematurely discontinue the study for other reasons, additional replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator. Replacement participants are individuals who have met inclusion into the study but have not been dosed at the discretion of the PI.

Replacement participants will receive both Regimens A and B, and will receive them in the same order as planned for the original participant and the minimum washout period of 7 days between dosing will be respected.

## **5.3. Participant and Study Completion**

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoA (i.e. the follow-up visit).

The end of the study is defined as the date of the last visit of the last participant in the study.

## **5.4. Scientific Rationale for Study Design**

The current bis-hydrochloride salt capsule formulation of GSK3640254 that has been used in the FTIH study is not suitable for long term development due to its susceptibility to humidity; therefore, a mesylate salt capsule formulation has been generated for future development. This is a bridging study to assess the relative bioavailability of the mesylate salt capsule formulation compared with the bis-hydrochloride salt capsule formulation.

All doses of GSK3640254 in this study will be administered in the fed state, with dosing occurring within 5 minutes of completing a moderate calorie/fat meal, similar to the FTIH study and the future proof of concept study planned in HIV-infected participants. Data with a previous MI, GSK3532795, demonstrated that food was necessary to achieve dose proportional PK and target efficacious concentrations. Given the structural similarities, including solubility limitations, between GSK3532795 and GSK3640254, administration of GSK3640254 with food is expected to enhance its bioavailability. The impact of food on exposures to GSK3640254 will be assessed in a future Phase 1 study in healthy participants during clinical development.

A 2-period, 2-sequence crossover design has been selected as recommended by the European Medicines Agency (EMA) guidance on bioavailability and bioequivalence studies. In addition, participants will be randomized to treatment sequence to avoid any potential period effects. The study is open-label as the primary objective is to assess the PK and there are no concerns about introducing bias. The washout period of at least 7 days between each dose of study treatment is considered sufficient to avoid any carryover effect between treatment periods, based on the average preliminary half-life of GSK3640254 of 23 hours observed in the first time in human study.

As this is a Phase 1 study, the most relevant population is healthy participants which allows characterisation of safety, tolerability and PK in a homogenous population without potential biases from a patient population. The EMA recommends including participants aged 18 years and older with normal weight, who are non-smokers, without a history of alcohol or drug abuse. The latter criteria are proposed to avoid interaction on drug metabolism and to avoid non-compliance. Therefore, this study will enroll healthy male and female participants aged between 18 to 55 years of age.

The study treatment has been shown in vitro to bind progesterone receptor, and only preliminary animal reproductive studies have been conducted; therefore, only women of nonchildbearing potential will be eligible for inclusion in this study.

## **5.5. Dose Justification**

To date, single oral doses of 1, 3, 10, 30, 100, 200, 400 and 700 mg have been administered to healthy participants in the fed state. Preliminary data show these dose levels have been well tolerated with no SAEs reported. The majority of AEs reported were mild in severity and unrelated to study treatment.

Emerging PK data suggest that the anticipated effective daily dose range is between 80 mg and 360 mg based on the bis-hydrochloride salt capsule data. Based on an improved solubility of the mesylate salt formulation in simulated gastric fluid and the emerging animal PK data with the mesylate salt, it is possible that the extent of absorption of the mesylate salt formulation could be up to 2-fold higher than the bis-hydrochloride salt formulation.

Therefore, taking all of these factors into consideration, single oral doses of 200 mg have been selected for this study.

## **6. STUDY POPULATION**

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Quotient Sciences must have a full medical history from each participant's general practitioner (GP) within the last 12 months, prior to enrollment in the study.

Participants will be recruited from the Quotient Sciences panel or by direct advertising to the public.

Before participants are admitted to the clinic, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each participant has not participated in a study at another site within at least 3 months of the dosing date.

## **6.1. Inclusion Criteria**

Participants are eligible to be included in the study only if all of the following criteria apply:

### **Age**

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

### **Type of Participant and Disease Characteristics**

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

### **Weight**

3. Body weight  $\geq 50$  kg for men and  $\geq 45$  kg for women, and body mass index (BMI) within the range 19.0 to 32.0 kg/m<sup>2</sup> (inclusive).

### **Sex**

4. Male or female

#### **a. Male participants:**

A male participant must adhere to the contraception requirements as detailed in [Appendix 5](#) of this protocol during the treatment period and for at least 95 days after the last dose of study treatment and refrain from donating sperm during this period.

#### **b. Female participants:**

A female participant is eligible to participate if she is not a woman of childbearing potential (WOCBP) as defined in [Appendix 5](#)

### **Informed Consent**

5. Capable of giving signed informed consent as described in [Appendix 3](#) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Inclusion criteria [2](#) will also be assessed at admission/pre-dose.

## **6.2. Exclusion Criteria**

Participants are excluded from the study if any of the following criteria apply:

## Medical Conditions

1. History of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
2. History of clinically significant psychiatric disorders as judged by the investigator. Psychiatric disorder requiring pharmacologic treatment in the last 5 years.
3. Any positive (abnormal) response confirmed by the investigator on a screening clinician (or qualified designee) administered CSSRS.
4. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
5. History of GI surgery (with exception of appendectomy).
6. History of Cholecystectomy
7. Any history of GI ulceration (oesophageal, stomach, duodenal).
8. Any history of GI symptoms requiring treatment in the last 3 months.
9. History of unexplained vaginal bleeding, endometrial hyperplasia with atypia or endometrial carcinoma.
10. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active.
11. ALT >1.5x ULN.
12. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35% of total).
13. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
14. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
15. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 or >100 bpm	<50 or >100 bpm
PR interval	<120 or >220 msec	
QRS duration	<70 or >120 msec	
QTcF interval	>450 msec	
Note: A heart rate from 100 to 110 bpm can be re-checked by ECG or vital signs within 30 minutes to verify eligibility.		

16. Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).

17. Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
18. Sinus Pauses >3 seconds.
19. Any significant arrhythmia which, in the opinion of the Investigator OR GSK/ViiV Medical Monitor, will interfere with the safety for the individual participant.
20. Non-sustained or sustained ventricular tachycardia (<sup>3</sup>3 consecutive ventricular ectopic beats).

**Prior/Concomitant Therapy**

21. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing (paracetamol/acetaminophen [up to 2 g per day] and 2.5% Hydrocortisone [for ECG lead contact dermatitis] is permitted any time during the study).

**Prior/Concurrent Clinical Study Experience**

22. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56 day period; therefore donation or loss of greater than 400 mL of blood within the previous 3 months.
23. Current enrollment or past participation within the last 3 months before signing of consent in this or any other clinical study involving an investigational study treatment or any other type of medical research.
24. Participants who have previously been enrolled in this study.

**Diagnostic assessments**

25. Presence of Hepatitis B surface antigen (HBsAg) at screening or positive Hepatitis C antibody test result at screening or within 3 months prior to first dose.
26. Confirmed positive pre-study drug/alcohol screen.
27. Positive HIV antibody test.
28. Regular use of known drugs of abuse, or history of drug or alcohol abuse in the past 5 years.

**Other Exclusions**

29. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer or 1 (25 mL) measure of spirits. One glass (125 mL) of wine is equivalent to 1.5 to 2 units, depending on type)
30. Current use or history of regular use of tobacco- or nicotine-containing products within 6 months prior to screening. A confirmed carbon monoxide breath test reading of greater than 10 ppm.

31. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
32. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
33. Participants who do not have the ability to swallow size 00 capsules.
34. Participants who are study site employees, or immediate family members of a study site or sponsor employee.

Exclusion criteria 1, 11, 12, 15, 17, 18, 19, 20, 21, and 26, from the list above will be reassessed at admission/pre-dose Period 1.

### **6.3. Lifestyle Restrictions**

#### **6.3.1. Meals and Dietary Restrictions**

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from Seville oranges and grapefruit derivatives for 24 hours before admission to each study period until after collection of the final PK sample in that period.
- Refrain from consumption of poppy seeds for 48 hours before screening, and from 48 hours before admission to each study period until after collection of the final PK sample in that period.
- Participants will be required to fast for at least 8 hours prior to dosing on Day 1 of each period. On the morning of Day 1, participants will be provided with a moderate calorie/fat breakfast. The breakfast will be consumed over a maximum period of 25 min, with dosing occurring approximately 30 min after the start of breakfast. Participants will be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some participants will take less time to eat, but dosing will still occur approximately 30 min after the start of breakfast. Lunch will be provided approximately 4 hours after dosing, an evening meal will be provided approximately 10 hours after dosing and an evening snack will be provided approximately 14 hours after dosing. Participants will consume at least 80% of the breakfast in order to be eligible for dosing in each period. The start and stop time of the meal will be recorded in the source documents and where less than 100% of the meal has been consumed, the percentage consumed will be recorded in the source documents.
- Other than liquid provided with breakfast and dosing, participants will refrain from drinking for 1 hour prior to dosing until 1 hour after dosing.
- Water will be allowed ad libitum from 1 hour post-dose. Decaffeinated fluid will be allowed from 4 hours post-dose.

#### **6.3.2. Caffeine, Alcohol, and Tobacco**

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before admission until after collection of the final PK sample in that period.



- Participants will abstain from alcohol for 24 hours before screening. During each dosing session, participants will abstain from alcohol from 24 hours before admission until after collection of the final PK sample in that period.
- Current smokers or users of other tobacco products will not be enrolled in this study.

#### **6.3.3. Activity**

- Participants will abstain from strenuous exercise for 72 hours before screening and then from 72 hours before admission until discharge from the study. Participants may participate in light recreational activities during studies (eg, watching television, reading).

#### **6.4. Screen Failures**

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the investigator if the reasons for the screening failure are expected to be temporary. Rescreened participants will be assigned a new screening number and will be re-consented.

### **7. TREATMENTS**

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

### 7.1. Treatments Administered

Regimen	A	B
<b>Study Treatment Name:</b>	GSK3640254 Capsule, 100 mg	GSK3640254 Mesylate Salt Capsule, 100 mg
<b>Dosage formulation:</b>	Bis-Hydrochloride salt formulation capsule	Mesylate salt formulation capsule
<b>Unit dose strength(s)/Dosage level(s):</b>	100 mg / 200 mg	100 mg / 200 mg
<b>Route of Administration</b>	Oral	Oral
<b>Dosing instructions:</b>	2 capsules, on the morning of Day 1 following a moderate fat meal. Capsules will be administered with 240 mL water.	2 capsules, on the morning of Day 1 following a moderate fat meal. Capsules will be administered with 240 mL water.
<b>Packaging and Labelling</b>	Study Treatment will be provided in HDPE containers with polypropylene screw cap lids. Each HDPE container will be labelled as required per country requirement.	
<b>Manufacturer</b>	GSK	Quotient

### 7.2. Dose Modification

No dose modification is permitted in this study. If a participant does not tolerate the dose administered, then the participant will be withdrawn from the study.

### 7.3. Method of Treatment Assignment

This is an open-label, randomized study, therefore a randomization schedule will be produced.

Participants will be randomized immediately before administration of the first dose in Period 1.

On the morning of Day 1 of Period 1, participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the two treatment sequences of the study ([Table 3](#)), according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software.

Participant randomization numbers will be allocated to treatment sequence in a 1:1 ratio. The allocation will be balanced with 7 participants receiving each treatment sequence. Each participant will be dispensed study treatment, labelled with his/her unique randomization number, throughout the study.

**Table 3 Treatment Sequences**

Treatment Sequence	N	Period 1	Period 2
AB	7	Regimen A	Regimen B
BA	7	Regimen B	Regimen A

Regimen A: 200 mg as 2 x 100 mg GSK3640254 Capsule, 100mg (reference)

Regimen B: 200 mg as 2 x 100 mg GSK3640254 Mesylate Salt Capsule, 100 mg (test)

A treatment allocation list will be produced prior to dosing using the randomization schedule and will be retained in the investigator site file (ISF).

#### **7.4. Blinding**

This is an open-label study.

#### **7.5. Preparation/Handling/Storage/Accountability**

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the technical agreement.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## **7.6. Treatment Compliance**

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- Participants will be dosed at the site, and will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth and hands to ensure that the study treatment was ingested.

## **7.7. Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the case report form (CRF) along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor will be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of  $\leq 2$  grams/day and 2.5% Hydrocortisone (for EKG lead contact dermatitis), is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor (if appropriate) if required to treat AEs.

## **7.8. Treatment after the End of the Study**

There is no treatment after the end of the study.

# **8. DISCONTINUATION CRITERIA**

## **8.1. Discontinuation of Study Treatment**

A participant will be withdrawn from the study at any time:

- At his or her own request

- At the discretion of the Investigator or the Sponsor for safety (including lab abnormalities or intercurrent illness), psychiatric, compliance, or administrative reasons.
- Any SAE.
- Termination of the study by GSK/VH. Safety data will be reviewed by the Sponsor in-stream by single case and collectively. If a safety concerns arises, a decision about continuation of the study will be made.
- Loss of ability to freely provide consent due to treatment of either a psychiatric or physical (eg, infectious disease) illness
- Repeat non-adherence by the participant with the requirements of the protocol or treatment (as determined by Investigator in consultation with the Medical Monitor)

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

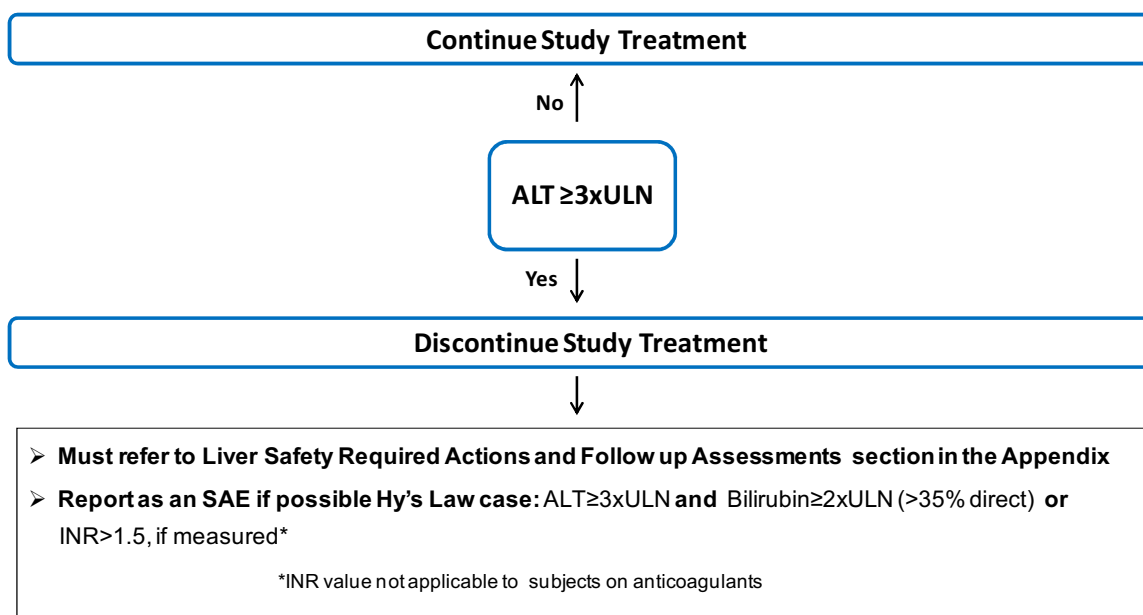
If a participant withdraws from the study, he/she must complete a follow-up visit.

#### **8.1.1. Liver Chemistry Stopping Criteria**

**Liver chemistry stopping and increased monitoring criteria** have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm below or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes that study treatment discontinuation is in the best interest of the participant.

## Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 7](#).

### 8.1.2. QTc Stopping Criteria

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. The formula to be used in this study is Fridericia's formula (i.e. QTcF). This formula may not be changed or substituted once the participant has been enrolled.

- The QTc will be based on single electrocardiograms.
- ECGs will be repeated if a participant has QTcF > 450 msec or > 30 msec increase from pre-dose in QTcF.

A participant that meets either bulleted criterion below based on the average of repeated ECG readings will be withdrawn from study treatment.

- QTcF > 500 msec
- Change from baseline (pre-dose Day 1) of QTcF > 60 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

### 8.1.3. Individual Safety Stopping Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator, after consultation with the medical monitor, is related to investigational product.
- The participant becomes pregnant.

- The participant initiates treatment with any prohibited medications.
- If any of the liver chemistry stopping criteria or QTc stopping criteria are met.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

#### **8.1.4. Temporary Discontinuation**

If a participant is not dosed when planned in a particular period (eg in case of unexpected personal circumstances or AEs that occur between treatment periods), they may be dosed at a later date (if a participant cannot re-attend within 28 days, they will be considered withdrawn), provided the following criteria are met:

- The AE has resolved or stabilized.
- The AE preventing dosing was not considered related to the study treatment.
- The participant has not met any individual stopping criteria.
- It is considered safe to continue to dose in the opinion of the investigator.

#### **8.1.5. Rechallenge**

##### **8.1.5.1. Study Treatment Restart or Rechallenge**

Study treatment restart or rechallenge after liver chemistry stopping criteria or any other withdrawal criteria are met by any participant in this study is not allowed.

#### **8.2. Withdrawal from the Study**

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records. The reason for withdrawal will be documented in the CRF.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A participant may be withdrawn at the Sponsor's request, for reasons such as significant protocol deviations or participant safety concern (and after discussion with the Investigator).
- If a participant is withdrawn from study treatment, this participant is also considered to be withdrawn from the study following completion of follow-up assessments.
- Participants will be withdrawn if the study is terminated.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

### 8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or will continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's CRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

### 8.4. Study Stopping Criteria

The study will be halted, and the risk to other participants evaluated, if any of the following criteria are met:

- Two participants experience an AE of Grade 3 intensity assessed as related to GSK3640254, by the principle investigator (PI).
- One participant experiences an AE of Grade 4 intensity assessed as related to GSK3640254, by the PI
- If greater than 25% of participants within the same period receiving GSK3640254 have a  $\geq$  Grade 3 intensity AE or laboratory abnormality (with the exception of asymptomatic changes in lipid panel) or a  $\geq$  Grade 2 intensity rash with concurrent fever, transaminase elevation or eosinophilia.
- There is one Serious Adverse Event (SAE) or death assessed as related to GSK3640254, by the PI.
- Two participants with confirmed QTcF  $\geq$  500 msec within the same period
- Two participants with clinically significant, in the opinion of the PI, arrhythmias within the same period
- Relatedness will be determined by the investigator. If the study is halted, a temporary halt will be submitted to the MHRA and EC in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC. Of note, the intensity of AEs will be determined using DAIDS criteria (see Section 12.4 for further details)



## 8.5. Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the principal investigator (PI) or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once exposure to GSK3640254 has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe AE(s), as defined in [Appendix 4](#), if considered to be related to study treatment.
- New information regarding the safety of the study treatment that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in [Section 3.3](#) demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances termination can only take place with the agreement of the investigator and sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

## 9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns will be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management or by generic screening (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL in a 4-week period.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- A participant will be allowed to leave the premises following completion of study-specific procedures at 48 hours post-dose providing that:
  - No AEs have been reported during the study visit
  - The participant responds positively when asked "How are you feeling?"

If any of these conditions are not met, then the participant may only be allowed to leave the clinical unit with the authorization of the investigator or appropriately qualified delegate.

## **9.1. Efficacy Assessments**

Not applicable.

## **9.2. Adverse Events**

The definitions of an AE or SAE can be found in Section 12.4. The intensity of AEs (and lab abnormalities) will be graded using the DAIDS Grading table. While the study population will consist of HIV-1 seronegative healthy volunteers, the DAIDS criteria will be used in later clinical trials (Phase 2a and beyond); additionally, the DAIDS criteria are have a more conservative grading scale relative to others (eg. CTCAE v 4.0). Thus, participant safety evaluation and monitoring will be more conservative.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

### **9.2.1. Time Period and Frequency for Collecting AE and SAE Information**

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).

- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in [Appendix 4](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 4](#).

#### **9.2.2. Method of Detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

#### **9.2.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in [Appendix 4](#).

#### **9.2.4. Regulatory Reporting Requirements for SAEs**

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### **9.2.5. Pregnancy**

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 90 days after the last dose.
- If a pregnancy is reported, the investigator will inform ViiV/GSK within 24 hours of learning of the pregnancy and will follow the procedures outlined in [Appendix 5](#).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

### **9.3. Treatment of Overdose**

For this study, any dose of GSK3640254 greater than that intended in this study will be considered an overdose.

There is no specific antidote for overdose with GSK3640254. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose, the investigator will:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3640254 can no longer be detected systemically (at least 72 hours after the last dose of GSK3640254).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor at 2, 4 and 6 hours post dose (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

### **9.4. Safety Assessments**

Planned time points for all safety assessments are provided in the SoA.

#### **9.4.1. Physical Examinations**

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI and neurological systems. Height and weight will also be measured and recorded.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

#### **9.4.2. Vital Signs**

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, heart rate and respiratory rate.
- The acceptable deviations from the nominal vital signs measurement time points are:
  - The pre-dose vital signs measurements will be taken  $\leq 2$  hours before dosing.
  - $\geq 0.5$  to 4 hours post-dose vital signs measurement will be taken within  $\pm 5$  minutes of the nominal post-dose sampling time
  - $>5$  to 12 hours post-dose vital signs measurement will be taken within  $\pm 10$  minutes of the nominal post-dose sampling time
  - $>12$  hours post-dose vital signs measurement will be taken within  $\pm 30$  min of the nominal post-dose sampling time if participants are resident in the clinic
  - For the return visit, vital signs measurements will be taken  $\pm 2$  hours from the nominal return visit time point.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), must be reported as an AE.

#### **9.4.3. Electrocardiograms**

- A single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- As noted in Section 8.1.2, ECGs will be repeated if a participant has QTcF  $> 450$  msec or  $> 30$  msec increase from pre-dose in QTcF. If the ECG is repeated, the QTc will be based on averaged QTc values of repeated ECGs obtained. Baseline QTc for the assessment of the withdrawal criteria will be the mean pre-dose QTcF of the relevant treatment period.
- The acceptable deviations from the nominal ECG measurement time points are:
  - The pre-dose ECG measurements will be taken  $\leq 2$  hours before dosing

- Post-dose ECG measurements will be taken  $\pm 15$  minutes from the nominal post-dose time point.
  - For the return visit, ECG measurements will be taken  $\pm 2$  hours from the nominal return visit time point.
- ECGs are to be measured after participant has been in a semi-supine position after approximately 5 minutes rest.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), will be reported as an AE.

#### **9.4.4. Clinical Safety Laboratory Assessments**

- Refer to [Appendix 2](#) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- Blood samples for scheduled laboratory assessments will be taken following an overnight fast of at least 8 hours.
- The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:
  - The pre-dose blood sample will be taken  $\leq 2$  hours before dosing
  - Post-dose blood samples will be taken  $\pm 1$  hour from the nominal blood sampling time except when the time point coincides with the PK blood sampling time. In this situation, the time window for the PK sample applies.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment will be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology will be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant

management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

#### **9.4.5. Suicidal Risk Monitoring**

GSK3640254 is not a CNS active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with previous MI GSK3532795, all participants will undergo screening using the CSSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator, will exclude them from participating. In the case of positive (abnormal) response confirmed by the investigator, the PI/Sub-investigator will arrange for urgent specialist psychiatric evaluation and management.

The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide Severity Rating Scale (C-SSRS; v4.1, 28 Apr 2010) [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment.

#### **9.5. Pharmacokinetics**

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the SoA (see Section 2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- The first 0.5 mL of blood withdrawn via cannula will be discarded.
- Processing, storage and shipping procedures are provided in the SRM or equivalent.
- The acceptable deviations from the nominal post-dose blood sampling times are as follows:
  - The pre-dose blood sample will be taken  $\leq 1$  hour before dosing.
  - $\geq 0.5$  to 4 hours post-dose samples will be taken within  $\pm 5$  minutes of the nominal post-dose sampling time
  - $>5$  to 12 hours post-dose samples will be taken within  $\pm 10$  minutes of the nominal post-dose sampling time
  - $>12$  hours post-dose samples will be taken within  $\pm 30$  min of the nominal post-dose sampling time if participants are resident in the clinic
  - The return visit (72 hours post-dose) sample will be taken within  $\pm 2$  hours of the nominal sampling time
- Samples will be used to evaluate the PK of GSK3640254. Samples collected for analyses of GSK3640254 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

- Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.
- Once the plasma has been analyzed for GSK3640254 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.
- Plasma analysis will be performed by PPD. Concentrations of GSK3640254 will be determined in plasma using the current approved bioanalytical methodology. Raw data will be archived at the Bioanalytical site as detailed in the SRM or equivalent.

## **9.6. Pharmacodynamics**

Pharmacodynamic parameters are not evaluated in this study.

## **9.7. Genetics**

Genetics are not evaluated in this study.

## **9.8. Biomarkers**

Biomarkers are not evaluated in this study.

## **9.9. Health Economics OR Medical Resource Utilization and Health Economics**

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# **10. STATISTICAL CONSIDERATIONS**

## **10.1. Sample Size Determination**

No formal sample size calculation has been made; however, based on experience from previous similar studies, 14 participants enrolled to achieve a minimum of 12 evaluable participants is considered sufficient.

Based on the emerging single-dose PK data from the FTIH study, the within-participant variability was 31.6% for C<sub>max</sub> and 36.8% for AUC(0-inf). Assuming a within-participant coefficient of variation (CV<sub>w</sub>) of 37% for C<sub>max</sub> and AUC(0-inf), and a sample size of 12 participants, it is estimated that the half width of the 90% confidence interval for the treatment difference on log-scale will be within 26% of the point estimate. If the point estimate of the ratio of geometric means is 1, then 90% confidence interval will be approximately (0.77,1.30) on the original scale.

## **10.2. Populations for Analyses**

For purposes of analysis, the following populations are defined:



Population	Description
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	Participants in the 'Safety Population' for whom a PK sample was obtained and analysed and will be the population for reporting of PK data.

### 10.3. Statistical Analyses

#### 10.3.1. Pharmacokinetic Analyses

No statistical hypotheses will be tested. All PK analyses will be performed on the PK Population.

Plasma GSK3640254 concentration-time data will be analysed by non-compartmental methods.

The plasma concentration-time data for each of the regimens will be used to determine the following PK parameters, as data permit:

- maximum observed plasma concentration ( $C_{\max}$ ).
- time to  $C_{\max}$  ( $T_{\max}$ ).
- the elapsed time from dosing at which GSK3640254 was first quantifiable in a concentration vs time profile ( $T_{\text{lag}}$ ).
- time from dosing at which GSK3640254 was last quantifiable in a concentration vs time profile ( $T_{\text{last}}$ ).
- observed plasma concentration at  $T_{\text{last}}$  ( $C_{\text{last}}$ ).
- observed concentration at 24 hours post-dose ( $C_{24\text{h}}$ ).
- area under the plasma concentration vs time curve ( $AUC_{(0-t_{\text{last}})}$  and  $AUC_{(0-\text{inf})}$ ).
- the percentage of AUC extrapolated beyond the last measured time point ( $AUC_{\% \text{extrap}}$ ).
- oral clearance, the apparent volume of plasma cleared of GSK3640254 per unit time following extravascular dosing ( $Cl/F$ )
- the apparent volume of distribution following extravascular dosing ( $V_d/F$ )
- terminal half-life ( $t_{1/2}$ ).
- Lambda-z

- relative bioavailability ( $F_{rel}$ ) of the GSK3640254 Mesylate Salt Capsule formulation (test) vs the GSK3640254 Capsule formulation (reference) based on  $AUC_{(0-inf)}$  (or  $AUC_{(0-tlast)}$  if  $AUC_{(0-inf)}$  can't be derived) and  $C_{max}$ .

Descriptive statistics (n, arithmetic mean, standard deviation [SD], 95% CI, minimum, median and maximum,) will be calculated by treatment for all PK concentrations over time and for the derived PK parameters. In addition, for loge-transformed PK parameter variables geometric mean, 95% CI and  $\%CV_b$  ( $100 * \sqrt{(\exp(SD^2) - 1)}$ ) will be provided, where the SD is the standard deviation of log-transformed data.

Endpoint	Statistical Analysis Methods
Primary	The primary PK endpoint is the comparison of the GSK3640254 Mesylate Salt Capsule formulation (test) with the GSK3640254 Capsule formulation (reference). Log transformed $AUC_{(0-inf)}$ , ( $AUC_{(0-tlast)}$ , if $AUC_{(0-inf)}$ cannot be derived), and $C_{max}$ values for GSK3640254 will be subjected to mixed effects modelling, including terms for period and treatment as fixed effects and participant as a random effect. The point estimate and associated 90% confidence interval (CIs) will be constructed for the difference, test treatment (B) – reference treatment (A). The point estimate and associated 90% CI will then be back-transformed to provide a point estimate and 90% CI for the ratio test/reference on the original scale.

### 10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	The safety endpoints will be summarized descriptively, and no formal statistical analysis will be conducted.

The Reporting and Analysis Plan will detail the content of the safety tables, figures and listings to be generated.

### 10.3.3. Interim Analyses

No formal statistical analyses or interim analyses are planned.

## 11. REFERENCES

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## 12. APPENDICES

### 12.1. Appendix 1: Abbreviations and Trademarks

#### List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ARV	Antiretroviral
AUC <sub>(0-inf)</sub>	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC <sub>(0-tlast)</sub>	Area under the concentration-time curve from zero to time of last sample taken
BMI	Body Mass Index
C24h	Concentration at 24 hour post-dose
CA	Competent authority
CI	Confidence Interval
C <sub>max</sub>	Maximum observed concentration
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DAIDS	Division of Acquired Immunodeficiency Syndrome
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
Frel	Relative bioavailability
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
Gag	Group-specific Antigen
GCP	Good Clinical Practice
GI	gastrointestinal
GP	General Practitioner
HBcAb	hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	investigator site file
MAD	Multiple Ascending Dose
MI	Maturation Inhibitor
MSDS	Material Safety Data Sheet
PK	Pharmacokinetics
PI	Principal investigator
QTcF	QT interval corrected for heart rate according to Fridericia's formula

SAD	Single Ascending Dose
SAEs	Serious Adverse Events
SD	Standard Deviation
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reactions
TOPS	The Over Volunteering Prevention System
TQT	Thorough QT
ULN	Upper Limit of Normal
WOCBP	Woman of Childbearing Potential

**Trademark Information**

<b>Trademarks of the GlaxoSmithKline group of companies</b>
NONE

<b>Trademarks not owned by the GlaxoSmithKline group of companies</b>
NONE

## 12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 4](#) will be performed at The Doctors Laboratory, with the exception of routine urinalysis, urine pregnancy test, urine drug screen, alcohol and carbon monoxide breath tests. These tests will be performed on-site.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 6](#) of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- All laboratory tests with values that are considered clinically significantly abnormal during participation in the study will be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Investigator, the etiology will be identified and the sponsor notified.

**Table 4 Protocol-Required Safety Laboratory Assessments**

Laboratory Assessments	Parameters			
Haematology	Platelet Count	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Haemoglobin (MCH) Mean Corpuscular Haemoglobin Concentration (MCHC) %Reticulocytes		<u>WBC count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red Blood Cell (RBC) Count			
	Haemoglobin			
	Haematocrit			
Clinical Chemistry <sup>1</sup>	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin (direct only if total is elevated)
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Chloride
	Bicarbonate			
	Routine Urinalysis	• Specific gravity		

Laboratory Assessments	Parameters
	<ul style="list-style-type: none"> <li>pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick</li> <li>Microscopic examination (if blood, leukocytes, nitrites or protein is abnormal)</li> </ul>
Other Screening Tests	<ul style="list-style-type: none"> <li>Follicle-stimulating hormone and estradiol (as needed in postmenopausal women only)</li> <li>Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)</li> <li>Alcohol breath test</li> <li>Carbon monoxide breath test</li> <li>Urine human chorionic gonadotropin (hCG) pregnancy test (for all women)</li> <li>Serology (HIV 1 and 2 antibodies, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)</li> </ul> <p>The results of each test must be entered into the CRF.</p>

## NOTES :

- Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 6. All events of ALT  $\geq 3 \times$  upper limit of normal (ULN) and bilirubin  $\geq 2 \times$  ULN ( $>35\%$  direct bilirubin) or ALT  $\geq 3 \times$  ULN and international normalized ratio (INR)  $>1.5$ , if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

## **12.3. Appendix 3: Study Governance Considerations**

### **Regulatory and Ethical Considerations**

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments to the protocol will require IEC/IRB and local regulatory approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SUSARs or other significant safety findings that occur on the study as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### **Protocol Amendments**

- After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.
- All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.
- If the participant information sheet (PIS) and ICF are updated as a result of an amendment, the new versions will be used to re-consent currently enrolled participants and must be provided to additional participants prior to their entry into the study.



## Protocol Deviations

- The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances will be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.
- Protocol waivers are not acceptable.
- Deviations from the protocol will be recorded in the source workbook as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.
- Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria stated in Section 8 have been met.

## Financial Disclosure

- Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## Informed Consent Process

- Participants will be provided with a written explanation of the study at least one day before the screening visit.
- The investigator or his/her representative will explain the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation to the participant and answer all questions regarding the study. Participants will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC.
- The CRF must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

**Data Protection**

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor and by inspectors from regulatory authorities.

**Publication Policy**

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

**Dissemination of Clinical Study Data**

- Following completion of the study, a clinical study report will be prepared.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with ViiV Healthcare policy and will be made available to the EC/MHRA within 1 year of the declaration of the end of trial.

**Data Quality Assurance**

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

### **Source Documents**

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- A study-specific source documentation list will be finalized by the sponsor before the start of the clinical phase of the study. The document will identify what data will be considered source data for this study.

### **Declaration of the End of the Study**

- The definition of the end of the study is defined as the last visit of the last participant (eg follow-up assessment). Any changes to this definition will be notified as a substantial amendment.
- The EC and MHRA will be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

### **Study and Site Closure**

ViiV Healthcare or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of ViiV Healthcare. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

## 12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definition of AE

AE Definition
<ul style="list-style-type: none"> <li>An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.</li> <li>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.</li> </ul>

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"> <li>Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).</li> <li>Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li> <li>New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses will be reported regardless of sequelae.</li> </ul>

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> <li>Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.</li> <li>The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.</li> <li>Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li> <li>Situations in which an untoward medical occurrence did not occur (social and/or</li> </ul>

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

**A SAE is defined as any untoward medical occurrence that, at any dose:**

### **a. Results in death**

### **b. Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

### **c. Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

### **d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

### **e. Is a congenital anomaly/birth defect**

### **f. Other situations:**

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the

other outcomes listed in the above definition. These events will usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### Definition of an Adverse Drug Reaction (ADR)

**An ADR is defined as an untoward medical occurrence that, at any dose:**

- Where a causal relationship with study treatment is at least a reasonable possibility (possibly related or related)

### Definition of a SUSAR

**A SUSAR is defined as any untoward medical occurrence that, at any dose:**

- Is believed to be related to study treatment and is both unexpected (ie the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the MHRA, European Medicines Agency (EMA), EC (see [Appendix 7](#))

### Recording AE and SAE

#### AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF (ie the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study treatment and the event).
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

### Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during using the DAIDS grading table ([http://rsc.tech-res.com/docs/default-source/safety/daids\\_ae\\_grading\\_table\\_v2\\_nov2014.pdf](http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf)) and assign it to 1 of the following categories: Events):

- Grade 1, Mild: no or minimal interference with usual social & functional activities.
- Grade 2, Moderate: greater than minimal interference with usual social & functional activities.
- Grade 3, Severe: inability to perform usual social & functional activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- Grade 4, Life Threatening: inability to perform basic self-care functions
- Grade 5, Death

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.



**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

**Reporting of SAE to GSK****SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the Communication Plan.

**SAE Reporting to GSK via Paper CRF**

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by

telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Communication Plan.

## **12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information**

### **Definitions**

#### **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

#### **Women in the following categories are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

### **Contraception Guidance**

#### **Male participants**

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame

- Refrain from donating sperm for duration of study and for 90 days after study completion or from last dose

### Female participants

Female participants who are not of childbearing potential do not need to use any methods of contraception.

Female participants of childbearing potential are not eligible to participate in this study.

Female participants will not participate in egg donation from dosing, for the duration of the study and for at least 28 days after the last dose of study treatment.

**Table 5      Highly Effective Contraceptive Methods**

<p><b>Highly Effective Contraceptive Methods That Are User Dependent <sup>a</sup></b>  <i>Failure rate of &lt;1% per year when used consistently and correctly.</i></p>
<p>Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> <li>• oral</li> <li>• intravaginal</li> <li>• transdermal</li> </ul>
<p>Progestogen-only hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> <li>• injectable</li> </ul>
<p><b>Highly Effective Methods That Are User Independent</b></p>
<ul style="list-style-type: none"> <li>• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation</li> <li>• Intrauterine device (IUD)</li> <li>• Intrauterine hormone-releasing system (IUS)</li> <li>• bilateral tubal occlusion</li> </ul>
<p>Vasectomized partner</p> <p><i>(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)</i></p>
<p>Sexual abstinence</p> <p><i>(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)</i></p>

**NOTES:**

- a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

**Pregnancy Testing**

- Urine pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the SureScreen Diagnostics test in accordance with instructions provided in its package insert at screening and admission to each study period

**Collection of Pregnancy Information****Male participants with partners who become pregnant**

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

**Female Participants who become pregnant**

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in [Appendix 4](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

## 12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

### Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
<b>ALT-absolute</b>	<p>ALT<math>\geq</math>3xULN</p> <p>If ALT<math>\geq</math>3xULN <b>AND</b> bilirubin<sup>1,2</sup> <math>\geq</math> 2xULN (&gt;35% direct bilirubin) or INR &gt;1.5, Report as an SAE.</p> <p>See additional Actions and Follow Up Assessments listed below</p>
Required Actions and Follow up Assessments	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study treatment</li> <li>• Report the event to GSK <b>within 24 hours</b></li> <li>• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE<sup>2</sup></li> <li>• Perform liver event follow up assessments</li> <li>• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> </ul> <p><b>MONITORING:</b></p> <p><b>If ALT<math>\geq</math>3xULN AND bilirubin <math>\geq</math> 2xULN or INR &gt;1.5</b></p> <ul style="list-style-type: none"> <li>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24 hrs</b></li> <li>• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>• A specialist or hepatology consultation is recommended</li> </ul> <p><b>If ALT<math>\geq</math>3xULN AND bilirubin &lt; 2xULN and INR <math>\leq</math>1.5:</b></p> <ul style="list-style-type: none"> <li>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</li> </ul>	<ul style="list-style-type: none"> <li>• Viral hepatitis serology<sup>3</sup></li> <li>• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend</li> <li>• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 2 days of last dose<sup>4</sup></li> <li>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>• Fractionate bilirubin, if total bilirubin<math>\geq</math>2xULN</li> <li>• Obtain complete blood count with differential to assess eosinophilia</li> <li>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</li> <li>• Record use of concomitant medications on the concomitant medications report form including paracetamol/acetaminophen, herbal remedies, other over the counter medications.</li> <li>• Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b>If ALT<math>\geq</math>3xULN AND bilirubin <math>\geq</math> 2xULN or INR &gt;1.5:</b></p>

Liver Chemistry Stopping Criteria	
<p>liver event follow up assessments within <b>24-72 hrs</b></p> <ul style="list-style-type: none"> <li>Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline</li> </ul>	<ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.</li> <li>Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. <b>NOTE: not required in China.</b></li> <li>Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.</li> </ul>

1. Serum bilirubin fractionation will be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT  $\geq$  3xULN and bilirubin  $\geq$  2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT  $\geq$  3xULN and bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

## References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et.al.. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.



## **12.7. Appendix 7: Safety Reporting to Ethics Committee and Regulatory Authorities**

### **Events Requiring Expedited Reporting**

SUSARs are subject to expedited reporting to the MHRA, EMA and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of a study treatment or that would be sufficient to consider changes in the study treatments administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the participant has completed the clinical study where the sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the study treatments and likely to affect the safety of the participants, such as:
  - an SAE which could be associated with the study procedures and which could modify the conduct of the study
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - any anticipated end or temporary halt of a study for safety reasons and conducted with the same study treatments in another country by the same sponsor

### **Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

### **Expedited Reporting of Events**

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures will be followed.

#### **Fatal or life-threatening SUSARs**

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. This responsibility will be delegated to the pharmacovigilance provider, GSK/ViiV.

The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

Any additional relevant information will be sent within 8 days of the report.

### **Other SUSARs**

It is the responsibility of the sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility will be delegated to the pharmacovigilance provider, GSK/ViiV.

The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

Any additional relevant information will be sent within 8 days of the report.

### **Urgent Safety Measures**

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of participants enrolled in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study participants.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the EC.

### **Reporting of Urgent Safety Issues**

Quotient Sciences is required to inform the appropriate competent authorities and the EC within 3 calendar days of the urgent safety issue.

### **Serious Breaches**

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the participants of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

**TITLE PAGE**

**Protocol Title:** A single centre, 2-period, randomized, open-label Phase 1 study to assess the relative bioavailability of a mesylate salt capsule of GSK3640254 compared to a hydrochloride salt capsule in healthy participants

**Protocol Number:** 208131 (QCL118221) / 01

**Short Title:** A study to compare the relative bioavailability of two different formulations of GSK3640254

**Compound Number:** GSK3640254

**Sponsor Name and Legal Registered Address:**

ViiV Healthcare UK Limited  
980 Great West Road  
Brentford  
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**Medical Monitor Name and Contact Information:**

PPD [REDACTED] DO, MPH

PPD [REDACTED]

PPD [REDACTED] (USA)

**Regulatory Agency Identifying Number(s):** EudraCT Number 2018-001175-21

**Approval Date:** 29-MAY-2018

**SPONSOR SIGNATORY:**

PPD



PPD [Redacted], DO, MPH

Vice President and Head, Clinical Development

ViiV Chief Scientific and Medical Officer

5/29/2018  
Date

PPD



**PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE**

DOCUMENT HISTORY	
Document	Date
<i>Amendment 1</i>	29-MAY-2018
<i>Original Protocol</i>	13-APR-2018

**Amendment 1** 29-May-2018

**Overall Rationale for the Amendment:** The purpose of Amendment 1 is: 1) to further enhance neuropsychiatric safety monitoring by assessing subjects using the Columbia Suicide Severity Rating Scale during the study and at the end of the study, and 2) to align recommendations on Male contraception and sperm donation with the ongoing First Time in Human (FTIH) clinical trial (207187).

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
Section 2, Schedule of Activities	Subjects will be evaluated using the Columbia Suicide Severity Rating Scale (CSSRS) on Day 3 (of both Period 1 and 2)	More frequent monitoring further enhances subject monitoring of neuropsychiatric AEs (e.g. suicidality) during the trial and at the end of the trial.
Section 3.3.1. Risk Assessment	Participants will be assessed for CSSRS during study and at end of study as additional mitigation of the neurologic/psychiatric safety risk.	This change further enhances the evaluation and management of neuropsychiatric AEs (e.g. suicidality).
Section 6.1, Inclusion Criteria	Male subjects must agree to use contraception as detailed in Appendix 5 during the treatment period and for at least 14 weeks following the last dose. In addition, male participants must refrain from donating sperm during this period.	This change aligns recommendations on Male contraception and sperm donation with the ongoing FTIH clinical trial (207187)
Section 8.1, Discontinuation of Study Treatment	A subject will be withdrawn from the trial for the emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered CSSRS on Day 3 (Period 1 or 2)	This change further enhances management of treatment emergent neuropsychiatric AEs (e.g. suicidality) during the trial and at the end of the trial.
Section 9.4.5, Suicidal Risk Monitoring	A positive (abnormal) response to the CSSRS confirmed by the investigator will result in the PI/SI arranging for urgent specialist psychiatric evaluation and management.	This change further enhances the evaluation and management of neuropsychiatric AEs (e.g. suicidality).
Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information	Male subjects must refrain from donating sperm for duration of study and for 14 weeks after study completion or from last dose.	This change aligns recommendations on Male contraception and sperm donation with the ongoing FTIH clinical trial (207187)

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## 1. SYNOPSIS

**Protocol Title:** A single centre, 2-period, randomized, open-label Phase 1 study to assess the relative bioavailability of a mesylate salt capsule of GSK3640254 compared to a bis-hydrochloride salt capsule in healthy participants

**Short Title:** A study to compare the relative bioavailability of two different formulations of GSK3640254

**Rationale:** A First Time in Human (FTIH) study is in progress and has used the bis-hydrochloride salt immediate release capsule formulation of GSK3640254 administered following a moderate calorie and fat meal. However, the bis-hydrochloride salt formulation is not suitable for long term clinical development as it is susceptible to humidity. A mesylate salt capsule formulation of GSK3640254 has been generated for later phase development and commercialization. The aim of this relative bioavailability study is to compare the exposure of the mesylate salt capsule formulation of GSK3640254 (mentioned as GSK3640254 Mesylate Salt Capsule in regimens) with that of the bis-hydrochloride salt capsule formulation (mentioned as GSK3640254 Capsule in regimens) administered following a moderate calorie and fat meal.

### Objectives and Endpoints:

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> <li>To evaluate the pharmacokinetic (PK) profiles of GSK3640254 following administration of the mesylate salt capsule relative to that of the bis-hydrochloride salt capsule (reference) in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>GSK3640254 area under the curve from time zero to infinity (<math>AUC_{(0-\infty)}</math>), <math>AUC_{(0-tlast)}</math>, maximum observed concentration (<math>C_{max}</math>), Time to <math>C_{max}</math> (<math>T_{max}</math>), Concentration at 24 hours post-dose (<math>C_{24h}</math>), relative bioavailability (<math>F_{rel}</math>) based on AUC and <math>C_{max}</math></li> </ul>
Secondary	
<ul style="list-style-type: none"> <li>To provide additional information of the safety and tolerability of single doses of GSK3640254 in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and/or other safety biomarkers</li> </ul>

### Overall Design:

This is a Phase 1 study and will be conducted at a single centre. This study will include 2 treatment periods, during which each of the open-label treatments will be administered to each of the 2 treatment groups. It is planned to enroll 14 healthy participants.

**Number of Participants:**

Fourteen participants will be enrolled such that sufficient data will be available for at least 12 evaluable participants. An evaluable participant is a participant who has received both Regimens A and B, and has safety and PK data up to 72 hours post-dose.

Up to 7 replacement participants may be enrolled. The maximum number of participants that may be dosed is 21.

**Treatment Groups and Duration:**

Participants will receive a single oral dose of each study treatment (Regimens A and B) during each of the 2 inpatient periods, in a sequence of administration to be assigned via the randomization: AB or BA.

- Treatment Group AB: Regimen A is administered in Period 1, Regimen B is administered in Period 2.
- Treatment Group BA: Regimen B is administered in Period 1, Regimen A is administered in Period 2.

**Regimens:**

- Regimen A: An oral dose of 200 mg as 2 x 100 mg GSK3640254 Capsule, 100 mg (reference) following a moderate fat meal.
- Regimen B: An oral dose of 200 mg as 2 x 100 mg GSK3640254 Mesylate Salt Capsule, 100 mg (test) following a moderate fat meal.

Participants will receive the formulations in the morning after a moderate-fat breakfast (approximately 600 calories with approximately 30% of the calories from fat).

Each participant will be enrolled in the study for approximately 7 weeks, dependent on screening and washout duration between periods. Participation will include a screening evaluation within 28 days of first study treatment administration and 2 separate inpatient periods. Participants will be admitted to the clinic in the morning of the day before dosing (i.e. Day -1) for Periods 1 and 2, and in the evening of Day -1 for Period 2. Each inpatient period will consist of 4 days (Period 1, morning admission on Day -1) or 3 days (Period 2, evening admission on Day -1) and 3 nights followed by a return visit 72 hours post-dose.

There will be a minimum washout of 7 days between each dose of study treatment.

A follow-up visit will occur 7 to 10 days after the last dose of study treatment.

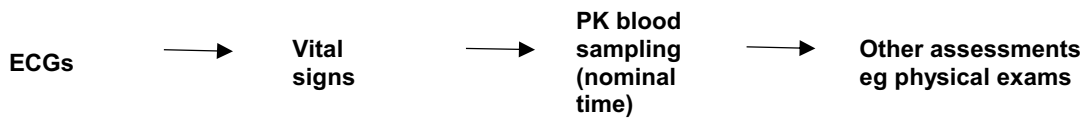
## 2. SCHEDULE OF ACTIVITIES (SOA)

The schedules of activities are presented in [Table 1](#). The time points for the PK blood sample collection, and ECG and vital sign assessments are presented in [Table 2](#).

The competent authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

The order of assessments will be:



Electrocardiograms will be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, e.g. physical examinations etc, will be performed within the required time windows. All safety assessments will be timed and performed relative to the start of dosing.

**Table 1 Schedule of Activities**

Procedure	Screening (up to 28 days before Day 1)	Treatment Periods 1 and 2 Day					Follow-up (7 to 10 days post last dose) or Early Discontinuation	Notes
		-1	1	2	3	4		
Outpatient visit	X					X	X	
Inpatient stay		X <sup>1</sup>	X	X	X <sup>2</sup>			1. Admission in the morning 2. Furlough from unit after assessments
Informed consent	X							
Inclusion and exclusion criteria	X	X <sup>3</sup>						3. Recheck clinical status at admission of Period 1
Demography	X							
Full physical examination including height and weight <sup>4</sup>	X							4. See Section 9.4.1 for systems to be examined
Columbia Suicide Severity Rating Scale (CSSRS)	X				X			
Brief physical examination			X <sup>5</sup>		X <sup>5</sup>		X	5. Pre-dose and 48 h post-dose See Section 9.4.1 for systems to be examined
Medical history (includes substance usage) <sup>6</sup>	X							6. Substances: Drugs, alcohol, tobacco and caffeine
Urine pregnancy test <sup>7</sup>	X	X					X	7. All female participants
Follicle stimulating hormone (FSH) <sup>8</sup>	X							8. As needed in women to confirm postmenopausal status
HIV, Hepatitis B and C screening	X							
Urine drug screen	X	X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Periods 1 and 2 Day					Follow-up (7 to 10 days post last dose) or Early Discontinuation	Notes
		-1	1	2	3	4		
Alcohol breath test	X	X						
Carbon monoxide breath test	X	X						
Laboratory assessments (haematology, clinical chemistry and urinalysis)	X	X <sup>9</sup>			X <sup>9</sup>		X	9. 48 h post-dose Allowable windows in Section 9.4.4
12-lead ECG	X	X	X <sup>10</sup>	X <sup>10</sup>		X <sup>10</sup>	X	10. Time points in Table 2 Allowable windows in Section 9.4.3
Vital signs	X	X	X <sup>11</sup>	X <sup>11</sup>		X <sup>11</sup>	X	11. Time points in Table 2 Allowable windows in Section 9.4.2
Randomization			X <sup>12</sup>					12. Pre-dose Period 1 only
Study treatment			X					
AE review		X	←=====→				X	
SAE review	X	X	←=====→				X	
Concomitant medication review		X	←=====→				X	
PK blood sample collection <sup>13</sup>			←=====→					13. Time points in Table 2

**Table 2      Pharmacokinetic Blood Sampling Collection, ECG and Vital Sign Times**

	Treatment Periods 1 and 2															
Time (h)	Pre-dose	0	0.5	1	1.5	2	3	4	5	6	8	12	24	36	48	72
Dosing		X														
PK Sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG (repeat allowed)	X					X		X		X			X			X
Single set of Vital signs	X					X		X		X			X			X

### 3. INTRODUCTION

GSK3640254 is a next-generation HIV-1 Maturation Inhibitor (MI); this novel class of anti-human immunodeficiency virus (HIV)-1 medicines prevents the maturation of HIV-1 virions by binding near a key structural element within the group-specific antigen (Gag) polyprotein that is required for virion maturation and assembly.

#### 3.1. Study Rationale

A First Time in Human (FTIH) study is in progress and has used the bis-hydrochloride salt immediate release capsule formulation of GSK3640254 administered following a moderate calorie and fat meal. However, the bis-hydrochloride salt formulation is not suitable for long term clinical development as it is susceptible to humidity. A mesylate salt capsule formulation of GSK3640254 has been identified for later phase development and commercialization. The aim of this relative bioavailability study is to compare the exposure of the mesylate salt capsule formulation of GSK3640254 with that of the bis-hydrochloride salt capsule formulation administered following a moderate calorie and fat meal.

#### 3.2. Background

Current therapy for HIV-infected individuals consists of a combination of approved antiretroviral (ARV) agents. More than twenty medicines are currently approved for HIV-1 infection, either as single agents, fixed-dose combinations or single-tablet regimens, the latter two containing 2 to 4 approved agents. Given the challenges inherent with the lifetime dosing of daily medications, there remains a need for new ARV agents that combine an optimal safety, tolerability and efficacy profile with a convenient dosing schedule. Significant toxicities have been described with each ARV agent in current use, and data continue to accumulate on the long-term clinical consequences of chronic ARV therapy [[Centers for Disease Control and Prevention](#), 2015; [Claessens](#), 2003; [Collins](#), 2006; [The DAD Study Group](#), 2007]. New ARV agents that offer an improved tolerability and safety profile are needed.

Despite the availability of different classes of ARV agents providing a variety of treatment options, treatment failure continues to occur as a result of high transmitted drug resistance, drug-associated toxicity and tolerability problems, and poor adherence to medication regimens. Although prevalence rates of drug resistance are falling in Western Europe, ~80% of HIV-infected patients who have received ARV therapy have resistance to at least one class of ARV [[De Luca](#), 2013]. Additionally, the prevalence of transmitted resistance to at least one ARV is ~10-17% in resource-rich regions, such as Europe [[WHO](#), 2012]. Unfortunately, resistance mutations selected by one ARV agent often confer resistance to multiple drugs in the same class, significantly limiting future therapeutic options. Later regimens often lack the convenience and tolerability of firstline drugs, which in turn exacerbates non-adherence. Thus, there is a continuing need for new classes of ARV drugs capable of providing potent, durable antiviral activity to a broad population of HIV-infected patients, with no cross-resistance to current agents, a relatively high barrier to the development of resistance on its own, and activity across diverse HIV-1 subtypes.

GSK3640254 is a next-generation HIV-1 Maturation Inhibitor (MI); this novel class of anti-HIV-1 medicines prevents the maturation of HIV-1 virions by binding near a key structural element within the Gag polyprotein that is required for virion maturation and assembly. MIs block the last protease cleavage event between Gag protein segments designated as 24-kilodalton HIV capsid protein p24 and spacer peptide 1. Blockage at this step results in the release of immature non-infectious virus particles. GSK3640254 has excellent potency and a broad pangenotypic spectrum in vitro. Laboratory studies confirm that GSK3640254 is an MI with a mechanism of action distinct from current ARVs, suggesting little if any risk of cross-resistance to current therapeutic agents.

As of 4 April 2018, the First Time in Human (FTIH) study is ongoing. It includes: 1) a single ascending dose (SAD) portion with doses of 1 mg to 700 mg (completed) and 2) a 14-day multiple ascending dose (MAD) portion (ongoing with 50 mg and 100 mg QD cohorts completed). The pharmacokinetics of GSK3640254 administered as a single dose following a moderate calorie/fat breakfast is characterized by a slow absorption with maximum concentration observed on average 3 to 4 hours after dosing. GSK3640254 is also slowly eliminated with an average half-life around 23 hours. C<sub>max</sub> and AUC tended to increase in a dose proportional manner from 1 mg to 400 mg with a less than dose proportional increase from 400 mg to 700 mg.

To support future toxicology studies to be conducted with the mesylate salt, single dose PK studies were conducted in male rats (doses of 10, 30 and 100 mg/kg) and male dogs (0.2, 1 and 5 mg/kg) with the mesylate salt. PK data were compared back to other PK studies conducted with the bis-hydrochloride salt. While the mesylate salt provided similar exposure as the bis-hydrochloride salt in dogs, the mesylate salt provided approximately a 75% increase in C<sub>max</sub> and AUC at the dose of 10 mg/kg with a smaller improvement of around 30% at the dose of 100 mg/kg in rats.

A detailed description of the chemistry, and the nonclinical pharmacology, pharmacokinetic and toxicology studies of GSK3640254 is provided in the Investigator's Brochure [GlaxoSmithKline Document Number [2016N294821\\_00](#)].

### **3.3. Benefit/Risk Assessment**

GSK3640254 is currently being studied in a Phase 1 SAD/MAD clinical trial in healthy participants to evaluate the safety, tolerability, and PK. The SAD portion of the study evaluating single doses ranging from 1 to 700 mg has been completed with preliminary data showing no major clinical safety or tolerability finding.

Until additional clinical safety information for GSK3640254 is available, precautions will be taken that are based on non-clinical safety assessment of GSK3640254 and reported clinical experiences of a previous, structurally similar maturation inhibitor (GSK3532795), in healthy and HIV-1 infected participants. Specifically, this previous maturation inhibitor (GSK3532795) was not progressed beyond Phase 2b clinical trials because of Grade 1-2 gastrointestinal intolerability (diarrhoea, abdominal pain) and treatment emergent resistance to study medications. In addition, two serious adverse events (SAEs; acute psychosis and suicidal/homicidal ideation) led to the early



termination of a Phase 1 Thorough QT (TQT) study in healthy participants at supratherapeutic doses.

Nonclinical findings with GSK3640254 have indicated the following potential risks for the clinical program: gastrointestinal (GI) intolerability/microscopic GI changes, cardiac conduction abnormalities (prolonged QT interval), hepatic injury (single cell necrosis), and renal changes (eosinophilic intracytoplasmatic inclusion bodies).

Until further preclinical studies on the effects of GSK3640254 on the reproductive system are available, it will be assumed that GSK3640254 has the potential to impair male and female fertility.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3640254 may be found in the Investigator's Brochure.

ViiV Healthcare has assessed this study for any risks that may be posed to participants taking part. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMA) guidance on strategies to identify and mitigate risks for FTIH clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07).

### 3.3.1. Risk Assessment

Potential risks of the IP (GSK3640254) are detailed below

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Investigational Product (IP) GSK3640254</b>		
GI intolerability/toxicity	<p><b><u>Non-clinical data:</u></b>            In a 14-day dose-range-finding study in rats, a non-tolerated dose of 300 mg/kg/day produced GI clinical signs and microscopic changes in the stomach and small intestine that were not seen at lower doses. These included minimal ulceration in the glandular stomach, minimal to moderate enterocyte vacuolation (lipid) in the duodenum, and minimal epithelial hyperplasia in the jejunum.            At tolerated doses, GI clinical signs occurred in rats (unformed faeces) at 100 mg/kg/day and dogs (sporadic vomiting and unformed, liquid or mucoid faeces) at <math>\geq 1</math> mg/kg/day.            At tolerated doses, reversible dose-responsive microscopic changes were observed in the stomachs of rats and dogs.</p>	<p><b><u>Participant selection:</u></b></p> <ul style="list-style-type: none"> <li>Participants with a clinically significant history of or current GI disorders will not be eligible to participate in this study</li> </ul> <p><b><u>Participant monitoring:</u></b></p> <ul style="list-style-type: none"> <li>Participants will be monitored for GI-related AEs</li> </ul>
Cardiac conduction abnormalities (prolonged QT interval)	<p><b><u>Non-clinical data:</u></b>            GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents with moderate potency. ECG changes attributed to GSK3640254 in telemeterized dogs at doses of 12.5 and 17</p>	<p><b><u>Participant selection:</u></b></p> <ul style="list-style-type: none"> <li>Participants with a history of or current cardiovascular disorders will not be eligible to participate in this study</li> <li>Participants with a QT interval corrected for heart rate according to Fridericia's formula</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>mg/kg consisted of increased rate-corrected QT interval from 3.5 to 6 hours post-dose (~ 9 msec) and during the overnight period (~ 6 msec). These QT effects were primarily limited to one dog given 17 mg/kg (<math>\leq 20</math> msec increase), with a plasma concentration of 7.96 <math>\mu\text{g/mL}</math> 8 hours after dosing.</p> <p>The no observed adverse effect level (NOAEL) in the study was 12.5 mg/kg, which produced similar systemic exposures (8.79 <math>\mu\text{g/mL}</math> 5 hours after dose).</p> <p>There were no GSK3640254-related effects on ECG parameters evaluated in the definitive general toxicity study in conscious restrained dogs given multiple doses of up to 25 mg/kg/day for 4 weeks.</p>	<p>(QTcF) &gt;450 msec at screening will not be eligible for this study</p> <p><b><u>Participant monitoring:</u></b></p> <ul style="list-style-type: none"> <li>• Participants will be monitored for cardiac-related AEs</li> <li>• ECGs will be monitored throughout the study</li> </ul>
Neurologic/psychiatric safety	<p><b><u>Clinical data:</u></b></p> <p>Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy participants in TQT study. From a neurologic and psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies, mild Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship was seen for</p>	<p><b><u>Participant selection:</u></b></p> <ul style="list-style-type: none"> <li>• Participants with a history of psychiatric disease requiring pharmacologic treatment in the last 5 years, any history of suicidal ideation (ever) or any clinically significant psychiatric history per investigator judgement will be excluded from the study</li> <li>• Protocol exclusion criterion and monitoring (during study and end of study) using assessment by the CSSRS. In the event of a positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the PI/Sub-</li> </ul>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>select neurologic and psychiatric AEs (based on TQT and P2b studies)</p> <p><b>Non-Clinical Data</b></p> <p>CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration</p>	<p>Investigator will arrange for urgent specialist psychiatric evaluation and management.</p> <ul style="list-style-type: none"> <li>Participants will undergo physical exams and continuous evaluation for adverse events during their participation in the trial.</li> </ul>

**Potential risks of study procedures are detailed below**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Study Procedures</b>		
Cannulation	During cannulation more than one attempt may be needed to insert the cannula in a vein of a participant and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.	<ul style="list-style-type: none"> <li>A vein assessment will be conducted at screening to ensure only volunteers with veins suitable for multiple venepuncture and cannulation are enrolled.</li> <li>Cannulation and venepuncture will only be performed by staff who are trained in these procedures</li> </ul>
Electrocardiograms	Electrocardiogram stickers on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove.	<ul style="list-style-type: none"> <li>Participants will be closely monitored to ensure any local irritation does not persist.</li> <li>2.5% hydrocortisone cream will be included in the list of permitted medication to relieve irritation from ECG leads.</li> </ul>

### 3.3.2. Benefit Assessment

There is no intended direct health benefit to the participants in this study.

### 3.3.3. Overall Benefit:Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the emerging clinical profile of GSK3640254 in the FTIH study, and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable.

## 4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b> <ul style="list-style-type: none"> <li>To evaluate the PK profiles of GSK3640254 following administration of the mesylate salt capsule relative to that of the bis-hydrochloride salt capsule (reference) in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>GSK3640254 area under the curve from time zero to infinity (<math>AUC_{(0-\infty)}</math>), <math>AUC_{(0-t_{last})}</math>, maximum observed concentration (<math>C_{max}</math>), Time to <math>C_{max}</math> (<math>T_{max}</math>), Concentration at 24 hours post-dose (<math>C_{24h}</math>), relative bioavailability (<math>F_{rel}</math>) based on AUC and <math>C_{max}</math></li> </ul>
<b>Secondary</b> <ul style="list-style-type: none"> <li>To provide additional information of the safety and tolerability of single doses of GSK3640254 in healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>AEs, clinical laboratory values, vital signs, ECGs, and/or other safety biomarkers</li> </ul>

## 5. STUDY DESIGN

### 5.1. Overall Design

This is a single centre, 2-period, randomized, open-label Phase 1 study. It is planned to enroll 14 healthy participants. It is planned to study 2 regimens (A and B) during 2 periods (1 and 2).

The following regimens will be administered during each period in the study:

- Regimen A: An oral dose of 200 mg as 2 x GSK3640254 Capsule, 100 mg (reference) following a moderate fat meal.
- Regimen B: An oral dose of 200 mg as 2 x GSK3640254 Mesylate Salt Capsule, 100 mg (test) following a moderate fat meal.

Each participant will receive each of the regimens (Regimens A and B) in a sequence during Period 1 and Period 2 as determined by the randomization:

- Randomized to AB: Regimen A administered in Period 1, followed by Regimen B in Period 2
- Randomized to BA: Regimen B administered in Period 1, followed by Regimen A in Period 2

Participants will receive a single oral dose of study treatment during each inpatient period. Participants will receive the formulations in the morning after a moderate-fat breakfast (approximately 600 calories with approximately 30% of the calories from fat).

#### Study Outline:

**Period 1:** Participants will be admitted to the clinical unit on the morning of the day before study treatment administration (Day -1) for Period 1. Participants will receive a single oral dose of the assigned study treatment regimen on Day 1 and will remain on site until 48 hours post-dose, and then return to the clinical unit for a 72 hours PK sample, vital signs and ECGs.

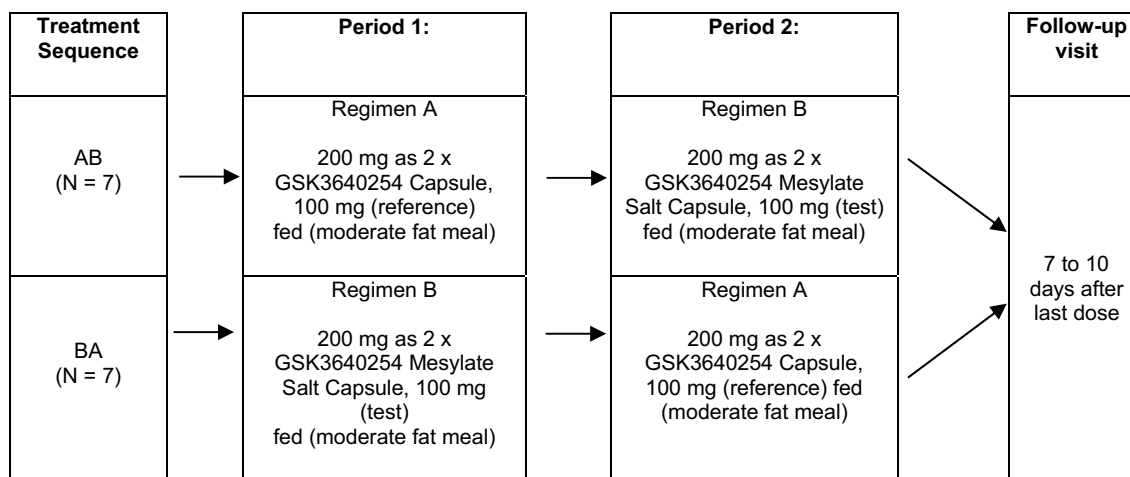
There will be a minimum washout of 7 days between each dose of study treatment.

**Period 2:** Participants will be admitted to the clinical unit on the morning of the day before study treatment administration (Day -1) for Period 2. Participants will receive a single oral dose of the assigned study treatment regimen on Day 1 and will remain on site until 48 hours post-dose, and then return to the clinical unit for a 72 hours PK sample, vital signs and ECGs.

**Follow up:** A Follow-up visit will be conducted 7 to 10 days after the last dose of study treatment.

The estimated maximum duration of the study from screening until follow-up for each participant is approximately 7 weeks.

**Figure 1 Study Design**



## **5.2. Number of Participants**

Fourteen participants will be enrolled such that sufficient data will be available for at least 12 evaluable participants. An evaluable participant is a participant who has received both Regimens A and B, and has safety and PK data up to 72 hours post-dose.

Up to 7 replacement participants may be enrolled. The maximum number of participants that may be dosed is 21.

Participants withdrawn by the investigator due to a moderate AE at least possibly related to study treatment will not be replaced. If participants prematurely discontinue the study for other reasons, additional replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator. Replacement participants are individuals who have met inclusion into the study but have not been dosed at the discretion of the PI.

Replacement participants will receive both Regimens A and B, and will receive them in the same order as planned for the original participant and the minimum washout period of 7 days between dosing will be respected.

## **5.3. Participant and Study Completion**

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoA (i.e. the follow-up visit).

The end of the study is defined as the date of the last visit of the last participant in the study.

## **5.4. Scientific Rationale for Study Design**

The current bis-hydrochloride salt capsule formulation of GSK3640254 that has been used in the FTIH study is not suitable for long term development due to its susceptibility to humidity; therefore, a mesylate salt capsule formulation has been generated for future development. This is a bridging study to assess the relative bioavailability of the mesylate salt capsule formulation compared with the bis-hydrochloride salt capsule formulation.

All doses of GSK3640254 in this study will be administered in the fed state, with dosing occurring within 5 minutes of completing a moderate calorie/fat meal, similar to the FTIH study and the future proof of concept study planned in HIV-infected participants. Data with a previous MI, GSK3532795, demonstrated that food was necessary to achieve dose proportional PK and target efficacious concentrations. Given the structural similarities, including solubility limitations, between GSK3532795 and GSK3640254, administration of GSK3640254 with food is expected to enhance its bioavailability. The impact of food on exposures to GSK3640254 will be assessed in a future Phase 1 study in healthy participants during clinical development.

A 2-period, 2-sequence crossover design has been selected as recommended by the European Medicines Agency (EMA) guidance on bioavailability and bioequivalence studies. In addition, participants will be randomized to treatment sequence to avoid any potential period effects. The study is open-label as the primary objective is to assess the PK and there are no concerns about introducing bias. The washout period of at least 7 days between each dose of study treatment is considered sufficient to avoid any carryover effect between treatment periods, based on the average preliminary half-life of GSK3640254 of 23 hours observed in the first time in human study.

As this is a Phase 1 study, the most relevant population is healthy participants which allows characterisation of safety, tolerability and PK in a homogenous population without potential biases from a patient population. The EMA recommends including participants aged 18 years and older with normal weight, who are non-smokers, without a history of alcohol or drug abuse. The latter criteria are proposed to avoid interaction on drug metabolism and to avoid non-compliance. Therefore, this study will enroll healthy male and female participants aged between 18 to 55 years of age.

The study treatment has been shown in vitro to bind progesterone receptor, and only preliminary animal reproductive studies have been conducted; therefore, only women of nonchildbearing potential will be eligible for inclusion in this study.

## **5.5. Dose Justification**

To date, single oral doses of 1, 3, 10, 30, 100, 200, 400 and 700 mg have been administered to healthy participants in the fed state. Preliminary data show these dose levels have been well tolerated with no SAEs reported. The majority of AEs reported were mild in severity and unrelated to study treatment.

Emerging PK data suggest that the anticipated effective daily dose range is between 80 mg and 360 mg based on the bis-hydrochloride salt capsule data. Based on an improved solubility of the mesylate salt formulation in simulated gastric fluid and the emerging animal PK data with the mesylate salt, it is possible that the extent of absorption of the mesylate salt formulation could be up to 2-fold higher than the bis-hydrochloride salt formulation.

Therefore, taking all of these factors into consideration, single oral doses of 200 mg have been selected for this study.

## **6. STUDY POPULATION**

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Quotient Sciences must have a full medical history from each participant's general practitioner (GP) within the last 12 months, prior to enrollment in the study.

Participants will be recruited from the Quotient Sciences panel or by direct advertising to the public.



Before participants are admitted to the clinic, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each participant has not participated in a study at another site within at least 3 months of the dosing date.

## 6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

### Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

### Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

### Weight

3. Body weight  $\geq 50$  kg for men and  $\geq 45$  kg for women, and body mass index (BMI) within the range 19.0 to 32.0 kg/m<sup>2</sup> (inclusive).

### Sex

4. Male or female

#### a. Male participants:

- b. A male participant must agree to use contraception as detailed in 12.5 of this protocol during the treatment period and for at least 14 weeks following the last dose, corresponding to the time needed to eliminate study treatment for potential genotoxic and teratogenic study treatments plus an additional 90 days (spermatogenesis cycle). In addition, male participants must refrain from donating sperm during this period.

#### Female participants:

A female participant is eligible to participate if she is not a woman of childbearing potential (WOCBP) as defined in [Appendix 5](#)

### Informed Consent

5. Capable of giving signed informed consent as described in [Appendix 3](#) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Inclusion criteria 2 will also be assessed at admission/pre-dose.

## 6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

## Medical Conditions

1. History of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
2. History of clinically significant psychiatric disorders as judged by the investigator. Psychiatric disorder requiring pharmacologic treatment in the last 5 years.
3. Any positive (abnormal) response confirmed by the investigator on a screening clinician (or qualified designee) administered CSSRS.
4. History or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
5. History of GI surgery (with exception of appendectomy).
6. History of Cholecystectomy
7. Any history of GI ulceration (oesophageal, stomach, duodenal).
8. Any history of GI symptoms requiring treatment in the last 3 months.
9. History of unexplained vaginal bleeding, endometrial hyperplasia with atypia or endometrial carcinoma.
10. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active.
11. ALT >1.5x ULN.
12. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35% of total).
13. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
14. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
15. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 or >100 bpm	<50 or >100 bpm
PR interval	<120 or >220 msec	
QRS duration	<70 or >120 msec	
QTcF interval	>450 msec	
Note: A heart rate from 100 to 110 bpm can be re-checked by ECG or vital signs within 30 minutes to verify eligibility.		

16. Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).

17. Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
18. Sinus Pauses >3 seconds.
19. Any significant arrhythmia which, in the opinion of the Investigator OR GSK/ViiV Medical Monitor, will interfere with the safety for the individual participant.
20. Non-sustained or sustained ventricular tachycardia (3 consecutive ventricular ectopic beats).

**Prior/Concomitant Therapy**

21. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing (paracetamol/acetaminophen [up to 2 g per day] and 2.5% Hydrocortisone [for ECG lead contact dermatitis] is permitted any time during the study).

**Prior/Concurrent Clinical Study Experience**

22. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56 day period; therefore donation or loss of greater than 400 mL of blood within the previous 3 months.
23. Current enrollment or past participation within the last 3 months before signing of consent in this or any other clinical study involving an investigational study treatment or any other type of medical research.
24. Participants who have previously been enrolled in this study.

**Diagnostic assessments**

25. Presence of Hepatitis B surface antigen (HBsAg) at screening or positive Hepatitis C antibody test result at screening or within 3 months prior to first dose.
26. Confirmed positive pre-study drug/alcohol screen.
27. Positive HIV antibody test.
28. Regular use of known drugs of abuse, or history of drug or alcohol abuse in the past 5 years.

**Other Exclusions**

29. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer or 1 (25 mL) measure of spirits. One glass (125 mL) of wine is equivalent to 1.5 to 2 units, depending on type)
30. Current use or history of regular use of tobacco- or nicotine-containing products within 6 months prior to screening. A confirmed carbon monoxide breath test reading of greater than 10 ppm.

31. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
32. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
33. Participants who do not have the ability to swallow size 00 capsules.
34. Participants who are study site employees, or immediate family members of a study site or sponsor employee.

Exclusion criteria 1, 11, 12, 15, 17, 18, 19, 20, 21, and 26, from the list above will be re-assessed at admission/pre-dose Period 1.

### **6.3. Lifestyle Restrictions**

#### **6.3.1. Meals and Dietary Restrictions**

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from Seville oranges and grapefruit derivatives for 24 hours before admission to each study period until after collection of the final PK sample in that period.
- Refrain from consumption of poppy seeds for 48 hours before screening, and from 48 hours before admission to each study period until after collection of the final PK sample in that period.
- Participants will be required to fast for at least 8 hours prior to dosing on Day 1 of each period. On the morning of Day 1, participants will be provided with a moderate calorie/fat breakfast. The breakfast will be consumed over a maximum period of 25 min, with dosing occurring approximately 30 min after the start of breakfast. Participants will be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some participants will take less time to eat, but dosing will still occur approximately 30 min after the start of breakfast. Lunch will be provided approximately 4 hours after dosing, an evening meal will be provided approximately 10 hours after dosing and an evening snack will be provided approximately 14 hours after dosing. Participants will consume at least 80% of the breakfast in order to be eligible for dosing in each period. The start and stop time of the meal will be recorded in the source documents and where less than 100% of the meal has been consumed, the percentage consumed will be recorded in the source documents.
- Other than liquid provided with breakfast and dosing, participants will refrain from drinking for 1 hour prior to dosing until 1 hour after dosing.
- Water will be allowed ad libitum from 1 hour post-dose. Decaffeinated fluid will be allowed from 4 hours post-dose.

#### **6.3.2. Caffeine, Alcohol, and Tobacco**

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before admission until after collection of the final PK sample in that period.

- Participants will abstain from alcohol for 24 hours before screening. During each dosing session, participants will abstain from alcohol from 24 hours before admission until after collection of the final PK sample in that period.
- Current smokers or users of other tobacco products will not be enrolled in this study.

#### **6.3.3. Activity**

- Participants will abstain from strenuous exercise for 72 hours before screening and then from 72 hours before admission until discharge from the study. Participants may participate in light recreational activities during studies (eg, watching television, reading).

#### **6.4. Screen Failures**

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the investigator if the reasons for the screening failure are expected to be temporary. Rescreened participants will be assigned a new screening number and will be re-consented.

### **7. TREATMENTS**

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

### 7.1. Treatments Administered

Regimen	A	B
<b>Study Treatment Name:</b>	GSK3640254 Capsule, 100 mg	GSK3640254 Mesylate Salt Capsule, 100 mg
<b>Dosage formulation:</b>	Bis-Hydrochloride salt formulation capsule	Mesylate salt formulation capsule
<b>Unit dose strength(s)/Dosage level(s):</b>	100 mg / 200 mg	100 mg / 200 mg
<b>Route of Administration</b>	Oral	Oral
<b>Dosing instructions:</b>	2 capsules, on the morning of Day 1 following a moderate fat meal. Capsules will be administered with 240 mL water.	2 capsules, on the morning of Day 1 following a moderate fat meal. Capsules will be administered with 240 mL water.
<b>Packaging and Labelling</b>	Study Treatment will be provided in HDPE containers with polypropylene screw cap lids. Each HDPE container will be labelled as required per country requirement.	
<b>Manufacturer</b>	GSK	Quotient

### 7.2. Dose Modification

No dose modification is permitted in this study. If a participant does not tolerate the dose administered, then the participant will be withdrawn from the study.

### 7.3. Method of Treatment Assignment

This is an open-label, randomized study, therefore a randomization schedule will be produced.

Participants will be randomized immediately before administration of the first dose in Period 1.

On the morning of Day 1 of Period 1, participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the two treatment sequences of the study ([Table 3](#)), according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software.

Participant randomization numbers will be allocated to treatment sequence in a 1:1 ratio. The allocation will be balanced with 7 participants receiving each treatment sequence. Each participant will be dispensed study treatment, labelled with his/her unique randomization number, throughout the study.

**Table 3 Treatment Sequences**

Treatment Sequence	N	Period 1	Period 2
AB	7	Regimen A	Regimen B
BA	7	Regimen B	Regimen A

Regimen A: 200 mg as 2 x 100 mg GSK3640254 Capsule, 100mg (reference)

Regimen B: 200 mg as 2 x 100 mg GSK3640254 Mesylate Salt Capsule, 100 mg (test)

A treatment allocation list will be produced prior to dosing using the randomization schedule and will be retained in the investigator site file (ISF).

#### **7.4. Blinding**

This is an open-label study.

#### **7.5. Preparation/Handling/Storage/Accountability**

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the technical agreement.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## **7.6. Treatment Compliance**

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- Participants will be dosed at the site, and will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth and hands to ensure that the study treatment was ingested.

## **7.7. Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the case report form (CRF) along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor will be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of  $\leq 2$  grams/day and 2.5% Hydrocortisone (for EKG lead contact dermatitis), is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor (if appropriate) if required to treat AEs.

## **7.8. Treatment after the End of the Study**

There is no treatment after the end of the study.

# **8. DISCONTINUATION CRITERIA**

## **8.1. Discontinuation of Study Treatment**

A participant will be withdrawn from the study at any time:

- At his or her own request



- At the discretion of the Investigator or the Sponsor for safety (including lab abnormalities or intercurrent illness), psychiatric, compliance, or administrative reasons.
- Any SAE.
- Termination of the study by GSK/VH. Safety data will be reviewed by the Sponsor in-stream by single case and collectively. If a safety concerns arises, a decision about continuation of the study will be made.
- Loss of ability to freely provide consent due to treatment of either a psychiatric or physical (eg, infectious disease) illness
- Repeat non-adherence by the participant with the requirements of the protocol or treatment (as determined by Investigator in consultation with the Medical Monitor)
- Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered CSSRS on Day 3 (Period 1 or 2).

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

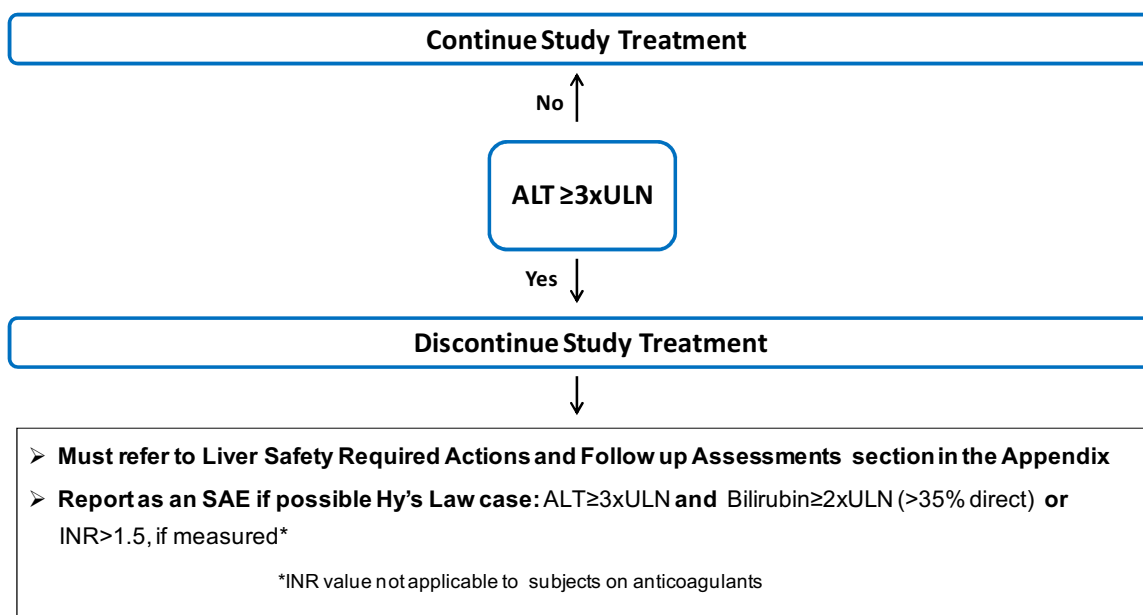
If a participant withdraws from the study, he/she must complete a follow-up visit.

#### **8.1.1. Liver Chemistry Stopping Criteria**

**Liver chemistry stopping and increased monitoring criteria** have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm below or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes that study treatment discontinuation is in the best interest of the participant.

## Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 7](#).

### 8.1.2. QTc Stopping Criteria

The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. The formula to be used in this study is Fridericia's formula (i.e. QTcF). This formula may not be changed or substituted once the participant has been enrolled.

- The QTc will be based on single electrocardiograms.
- ECGs will be repeated if a participant has QTcF > 450 msec or > 30 msec increase from pre-dose in QTcF.

A participant that meets either bulleted criterion below based on the average of repeated ECG readings will be withdrawn from study treatment.

- QTcF > 500 msec
- Change from baseline (pre-dose Day 1) of QTcF > 60 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

### 8.1.3. Individual Safety Stopping Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator, after consultation with the medical monitor, is related to investigational product.
- The participant becomes pregnant.

- The participant initiates treatment with any prohibited medications.
- If any of the liver chemistry stopping criteria or QTc stopping criteria are met.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

#### **8.1.4. Temporary Discontinuation**

If a participant is not dosed when planned in a particular period (eg in case of unexpected personal circumstances or AEs that occur between treatment periods), they may be dosed at a later date (if a participant cannot re-attend within 28 days, they will be considered withdrawn), provided the following criteria are met:

- The AE has resolved or stabilized.
- The AE preventing dosing was not considered related to the study treatment.
- The participant has not met any individual stopping criteria.
- It is considered safe to continue to dose in the opinion of the investigator.

#### **8.1.5. Rechallenge**

##### **8.1.5.1. Study Treatment Restart or Rechallenge**

Study treatment restart or rechallenge after liver chemistry stopping criteria or any other withdrawal criteria are met by any participant in this study is not allowed.

#### **8.2. Withdrawal from the Study**

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records. The reason for withdrawal will be documented in the CRF.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A participant may be withdrawn at the Sponsor's request, for reasons such as significant protocol deviations or participant safety concern (and after discussion with the Investigator).
- If a participant is withdrawn from study treatment, this participant is also considered to be withdrawn from the study following completion of follow-up assessments.
- Participants will be withdrawn if the study is terminated.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

### 8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or will continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's CRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

### 8.4. Study Stopping Criteria

The study will be halted, and the risk to other participants evaluated, if any of the following criteria are met:

- Two participants experience an AE of Grade 3 intensity assessed as related to GSK3640254, by the principle investigator (PI).
- One participant experiences an AE of Grade 4 intensity assessed as related to GSK3640254, by the PI
- If greater than 25% of participants within the same period receiving GSK3640254 have a  $\geq$  Grade 3 intensity AE or laboratory abnormality (with the exception of asymptomatic changes in lipid panel) or a  $\geq$  Grade 2 intensity rash with concurrent fever, transaminase elevation or eosinophilia.
- There is one Serious Adverse Event (SAE) or death assessed as related to GSK3640254, by the PI.
- Two participants with confirmed QTcF  $\geq$  500 msec within the same period
- Two participants with clinically significant, in the opinion of the PI, arrhythmias within the same period
- Relatedness will be determined by the investigator. If the study is halted, a temporary halt will be submitted to the MHRA and EC in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC. Of note, the intensity of AEs will be determined using DAIDS criteria (see Section 12.4 for further details)

## 8.5. Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the principal investigator (PI) or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once exposure to GSK3640254 has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe AE(s), as defined in [Appendix 4](#), if considered to be related to study treatment.
- New information regarding the safety of the study treatment that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in Section [3.3](#) demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances termination can only take place with the agreement of the investigator and sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

## 9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns will be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management or by generic screening (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL in a 4-week period.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- A participant will be allowed to leave the premises following completion of study-specific procedures at 48 hours post-dose providing that:
  - No AEs have been reported during the study visit
  - The participant responds positively when asked "How are you feeling?"

If any of these conditions are not met, then the participant may only be allowed to leave the clinical unit with the authorization of the investigator or appropriately qualified delegate.

## **9.1. Efficacy Assessments**

Not applicable.

## **9.2. Adverse Events**

The definitions of an AE or SAE can be found in Section 12.4. The intensity of AEs (and lab abnormalities) will be graded using the DAIDS Grading table. While the study population will consist of HIV-1 seronegative healthy volunteers, the DAIDS criteria will be used in later clinical trials (Phase 2a and beyond); additionally, the DAIDS criteria are have a more conservative grading scale relative to others (eg. CTCAE v 4.0). Thus, participant safety evaluation and monitoring will be more conservative.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

### **9.2.1. Time Period and Frequency for Collecting AE and SAE Information**

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).

- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in [Appendix 4](#) . The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 4](#) .

#### **9.2.2. Method of Detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

#### **9.2.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in [Appendix 4](#) .

#### **9.2.4. Regulatory Reporting Requirements for SAEs**

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### **9.2.5. Pregnancy**

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 90 days after the last dose.
- If a pregnancy is reported, the investigator will inform ViiV/GSK within 24 hours of learning of the pregnancy and will follow the procedures outlined in [Appendix 5](#).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

### **9.3. Treatment of Overdose**

For this study, any dose of GSK3640254 greater than that intended in this study will be considered an overdose.

There is no specific antidote for overdose with GSK3640254. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose, the investigator will:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3640254 can no longer be detected systemically (at least 72 hours after the last dose of GSK3640254).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor at 2, 4 and 6 hours post dose (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

### **9.4. Safety Assessments**

Planned time points for all safety assessments are provided in the SoA.

#### **9.4.1. Physical Examinations**

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI and neurological systems. Height and weight will also be measured and recorded.



- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

#### **9.4.2. Vital Signs**

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, heart rate and respiratory rate.
- The acceptable deviations from the nominal vital signs measurement time points are:
  - The pre-dose vital signs measurements will be taken  $\leq 2$  hours before dosing.
  - $\geq 0.5$  to 4 hours post-dose vital signs measurement will be taken within  $\pm 5$  minutes of the nominal post-dose sampling time
  - $>5$  to 12 hours post-dose vital signs measurement will be taken within  $\pm 10$  minutes of the nominal post-dose sampling time
  - $>12$  hours post-dose vital signs measurement will be taken within  $\pm 30$  min of the nominal post-dose sampling time if participants are resident in the clinic
  - For the return visit, vital signs measurements will be taken  $\pm 2$  hours from the nominal return visit time point.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), must be reported as an AE.

#### **9.4.3. Electrocardiograms**

- A single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- As noted in Section 8.1.2, ECGs will be repeated if a participant has QTcF  $> 450$  msec or  $> 30$  msec increase from pre-dose in QTcF. If the ECG is repeated, the QTc will be based on averaged QTc values of repeated ECGs obtained Baseline QTc for the assessment of the withdrawal criteria will be the mean pre-dose QTcF of the relevant treatment period.
- The acceptable deviations from the nominal ECG measurement time points are:
  - The pre-dose ECG measurements will be taken  $\leq 2$  hours before dosing

- Post-dose ECG measurements will be taken  $\pm 15$  minutes from the nominal post-dose time point.
  - For the return visit, ECG measurements will be taken  $\pm 2$  hours from the nominal return visit time point.
- ECGs are to be measured after participant has been in a semi-supine position after approximately 5 minutes rest.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), will be reported as an AE.

#### **9.4.4. Clinical Safety Laboratory Assessments**

- Refer to [Appendix 2](#) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- Blood samples for scheduled laboratory assessments will be taken following an overnight fast of at least 8 hours.
- The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:
  - The pre-dose blood sample will be taken  $\leq 2$  hours before dosing
  - Post-dose blood samples will be taken  $\pm 1$  hour from the nominal blood sampling time except when the time point coincides with the PK blood sampling time. In this situation, the time window for the PK sample applies.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment will be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology will be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant

management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

#### **9.4.5. Suicidal Risk Monitoring**

GSK3640254 is not a CNS active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with previous MI GSK3532795, all participants will undergo screening using the CSSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator, will exclude them from participating. Finally, participants will also have assessment by the CSSRS on Day 3 (of both Period 1 and 2) (see Section 2 SoA table for details). Any positive (abnormal) response confirmed by the investigator on Day 3 (of both Period 1 and 2) will result in their discontinuation. A positive (abnormal) response confirmed by the investigator will result in the PI/Sub-Investigator arranging for urgent specialist psychiatric evaluation and management.

The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide Severity Rating Scale (C-SSRS; v4.1, 28 Apr 2010) [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment.

#### **9.5. Pharmacokinetics**

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the SoA (see Section 2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- The first 0.5 mL of blood withdrawn via cannula will be discarded.
- Processing, storage and shipping procedures are provided in the SRM or equivalent.
- The acceptable deviations from the nominal post-dose blood sampling times are as follows:
  - The pre-dose blood sample will be taken  $\leq 1$  hour before dosing.
  - $\geq 0.5$  to 4 hours post-dose samples will be taken within  $\pm 5$  minutes of the nominal post-dose sampling time
  - $>5$  to 12 hours post-dose samples will be taken within  $\pm 10$  minutes of the nominal post-dose sampling time
  - $>12$  hours post-dose samples will be taken within  $\pm 30$  min of the nominal post-dose sampling time if participants are resident in the clinic
  - The return visit (72 hours post-dose) sample will be taken within  $\pm 2$  hours of the nominal sampling time

- Samples will be used to evaluate the PK of GSK3640254. Samples collected for analyses of GSK3640254 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.
- Once the plasma has been analyzed for GSK3640254 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.
- Plasma analysis will be performed by PPD. Concentrations of GSK3640254 will be determined in plasma using the current approved bioanalytical methodology. Raw data will be archived at the Bioanalytical site as detailed in the SRM or equivalent.

## **9.6. Pharmacodynamics**

Pharmacodynamic parameters are not evaluated in this study.

## **9.7. Genetics**

Genetics are not evaluated in this study.

## **9.8. Biomarkers**

Biomarkers are not evaluated in this study.

## **9.9. Health Economics OR Medical Resource Utilization and Health Economics**

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# **10. STATISTICAL CONSIDERATIONS**

## **10.1. Sample Size Determination**

No formal sample size calculation has been made; however, based on experience from previous similar studies, 14 participants enrolled to achieve a minimum of 12 evaluable participants is considered sufficient.

Based on the emerging single-dose PK data from the FTIH study, the within-participant variability was 31.6% for C<sub>max</sub> and 36.8% for AUC(0-inf). Assuming a within-participant coefficient of variation (CV<sub>w</sub>) of 37% for C<sub>max</sub> and AUC(0-inf), and a sample size of 12 participants, it is estimated that the half width of the 90% confidence interval for the treatment difference on log-scale will be within 26% of the point estimate. If the point estimate of the ratio of geometric means is 1, then 90% confidence interval will be approximately (0.77,1.30) on the original scale.

## 10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	Participants in the 'Safety Population' for whom a PK sample was obtained and analysed and will be the population for reporting of PK data.

## 10.3. Statistical Analyses

### 10.3.1. Pharmacokinetic Analyses

No statistical hypotheses will be tested. All PK analyses will be performed on the PK Population.

Plasma GSK3640254 concentration-time data will be analysed by non-compartmental methods.

The plasma concentration-time data for each of the regimens will be used to determine the following PK parameters, as data permit:

- maximum observed plasma concentration ( $C_{\max}$ ).
- time to  $C_{\max}$  ( $T_{\max}$ ).
- the elapsed time from dosing at which GSK3640254 was first quantifiable in a concentration vs time profile ( $T_{\text{lag}}$ ).
- time from dosing at which GSK3640254 was last quantifiable in a concentration vs time profile ( $T_{\text{last}}$ ).
- observed plasma concentration at  $T_{\text{last}}$  ( $C_{\text{last}}$ ).
- observed concentration at 24 hours post-dose ( $C_{24\text{h}}$ ).
- area under the plasma concentration vs time curve ( $\text{AUC}_{(0-\text{tlast})}$  and  $\text{AUC}_{(0-\text{inf})}$ ).
- the percentage of AUC extrapolated beyond the last measured time point ( $\text{AUC}_{\% \text{extrap}}$ ).
- oral clearance, the apparent volume of plasma cleared of GSK3640254 per unit time following extravascular dosing ( $\text{Cl/F}$ )
- the apparent volume of distribution following extravascular dosing ( $\text{Vd/F}$ )
- terminal half-life ( $t_{1/2}$ ).

- Lambda-z
- relative bioavailability ( $F_{rel}$ ) of the GSK3640254 Mesylate Salt Capsule formulation (test) vs the GSK3640254 Capsule formulation (reference) based on  $AUC_{(0-inf)}$  (or  $AUC_{(0-tlast)}$  if  $AUC_{(0-inf)}$  can't be derived) and  $C_{max}$ .

Descriptive statistics (n, arithmetic mean, standard deviation [SD], 95% CI, minimum, median and maximum,) will be calculated by treatment for all PK concentrations over time and for the derived PK parameters. In addition, for loge-transformed PK parameter variables geometric mean, 95% CI and  $\%CV_b$  ( $100 * \sqrt{(\exp(SD^2) - 1)}$ ) will be provided, where the SD is the standard deviation of log-transformed data.

Endpoint	Statistical Analysis Methods
Primary	The primary PK endpoint is the comparison of the GSK3640254 Mesylate Salt Capsule formulation (test) with the GSK3640254 Capsule formulation (reference). Log transformed $AUC_{(0-inf)}$ , ( $AUC_{(0-tlast)}$ , if $AUC_{(0-inf)}$ cannot be derived), and $C_{max}$ values for GSK3640254 will be subjected to mixed effects modelling, including terms for period and treatment as fixed effects and participant as a random effect. The point estimate and associated 90% confidence interval (CIs) will be constructed for the difference, test treatment (B) – reference treatment (A). The point estimate and associated 90% CI will then be back-transformed to provide a point estimate and 90% CI for the ratio test/reference on the original scale.

### 10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	The safety endpoints will be summarized descriptively, and no formal statistical analysis will be conducted.

The Reporting and Analysis Plan will detail the content of the safety tables, figures and listings to be generated.

### 10.3.3. Interim Analyses

No formal statistical analyses or interim analyses are planned.

## 11. REFERENCES

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## 12. APPENDICES

### 12.1. Appendix 1: Abbreviations and Trademarks

#### List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ARV	Antiretroviral
AUC <sub>(0-inf)</sub>	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC <sub>(0-tlast)</sub>	Area under the concentration-time curve from zero to time of last sample taken
BMI	Body Mass Index
C24h	Concentration at 24 hour post-dose
CA	Competent authority
CI	Confidence Interval
C <sub>max</sub>	Maximum observed concentration
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DAIDS	Division of Acquired Immunodeficiency Syndrome
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
Frel	Relative bioavailability
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
Gag	Group-specific Antigen
GCP	Good Clinical Practice
GI	gastrointestinal
GP	General Practitioner
HBcAb	hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	investigator site file
MAD	Multiple Ascending Dose
MI	Maturation Inhibitor
MSDS	Material Safety Data Sheet
PK	Pharmacokinetics
PI	Principal investigator
QTcF	QT interval corrected for heart rate according to Fridericia's formula



SAD	Single Ascending Dose
SAEs	Serious Adverse Events
SD	Standard Deviation
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reactions
TOPS	The Over Volunteering Prevention System
TQT	Thorough QT
ULN	Upper Limit of Normal
WOCBP	Woman of Childbearing Potential

**Trademark Information**

<b>Trademarks of the GlaxoSmithKline group of companies</b>
NONE

<b>Trademarks not owned by the GlaxoSmithKline group of companies</b>
None

## 12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 4](#) will be performed at The Doctors Laboratory, with the exception of routine urinalysis, urine pregnancy test, urine drug screen, alcohol and carbon monoxide breath tests. These tests will be performed on-site.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 6](#) of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- All laboratory tests with values that are considered clinically significantly abnormal during participation in the study will be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Investigator, the etiology will be identified and the sponsor notified.

**Table 4 Protocol-Required Safety Laboratory Assessments**

Laboratory Assessments	Parameters			
Haematology	Platelet Count	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Haemoglobin (MCH) Mean Corpuscular Haemoglobin Concentration (MCHC) %Reticulocytes		<u>WBC count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red Blood Cell (RBC) Count			
	Haemoglobin			
	Haematocrit			
Clinical Chemistry <sup>1</sup>	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin (direct only if total is elevated)
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Chloride
	Bicarbonate			
	Routine Urinalysis	• Specific gravity		

Laboratory Assessments	Parameters
	<ul style="list-style-type: none"> <li>pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick</li> <li>Microscopic examination (if blood, leukocytes, nitrites or protein is abnormal)</li> </ul>
Other Screening Tests	<ul style="list-style-type: none"> <li>Follicle-stimulating hormone and estradiol (as needed in postmenopausal women only)</li> <li>Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)</li> <li>Alcohol breath test</li> <li>Carbon monoxide breath test</li> <li>Urine human chorionic gonadotropin (hCG) pregnancy test (for all women)</li> <li>Serology (HIV 1 and 2 antibodies, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)</li> </ul> <p>The results of each test must be entered into the CRF.</p>

## NOTES :

- Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 6. All events of ALT  $\geq 3 \times$  upper limit of normal (ULN) and bilirubin  $\geq 2 \times$  ULN ( $>35\%$  direct bilirubin) or ALT  $\geq 3 \times$  ULN and international normalized ratio (INR)  $>1.5$ , if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

## **12.3. Appendix 3: Study Governance Considerations**

### **Regulatory and Ethical Considerations**

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments to the protocol will require IEC/IRB and local regulatory approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SUSARs or other significant safety findings that occur on the study as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### **Protocol Amendments**

- After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.
- All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.
- If the participant information sheet (PIS) and ICF are updated as a result of an amendment, the new versions will be used to re-consent currently enrolled participants and must be provided to additional participants prior to their entry into the study.

## Protocol Deviations

- The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances will be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.
- Protocol waivers are not acceptable.
- Deviations from the protocol will be recorded in the source workbook as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.
- Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria stated in Section 8 have been met.

## Financial Disclosure

- Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## Informed Consent Process

- Participants will be provided with a written explanation of the study at least one day before the screening visit.
- The investigator or his/her representative will explain the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation to the participant and answer all questions regarding the study. Participants will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC.
- The CRF must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

## Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor and by inspectors from regulatory authorities.

## Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## Dissemination of Clinical Study Data

- Following completion of the study, a clinical study report will be prepared.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with ViiV Healthcare policy and will be made available to the EC/MHRA within 1 year of the declaration of the end of trial.

## Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

### **Source Documents**

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- A study-specific source documentation list will be finalized by the sponsor before the start of the clinical phase of the study. The document will identify what data will be considered source data for this study.

### **Declaration of the End of the Study**

- The definition of the end of the study is defined as the last visit of the last participant (eg follow-up assessment). Any changes to this definition will be notified as a substantial amendment.
- The EC and MHRA will be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

### **Study and Site Closure**

ViiV Healthcare or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of ViiV Healthcare. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development



## 12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definition of AE

AE Definition
<ul style="list-style-type: none"> <li>An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.</li> <li>NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.</li> </ul>

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"> <li>Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).</li> <li>Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li> <li>New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li> <li>Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses will be reported regardless of sequelae.</li> </ul>

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> <li>Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.</li> <li>The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.</li> <li>Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li> <li>Situations in which an untoward medical occurrence did not occur (social and/or</li> </ul>

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

**A SAE is defined as any untoward medical occurrence that, at any dose:**

### **a. Results in death**

### **b. Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

### **c. Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

### **d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

### **e. Is a congenital anomaly/birth defect**

### **f. Other situations:**

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the

other outcomes listed in the above definition. These events will usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### Definition of an Adverse Drug Reaction (ADR)

**An ADR is defined as an untoward medical occurrence that, at any dose:**

- Where a causal relationship with study treatment is at least a reasonable possibility (possibly related or related)

### Definition of a SUSAR

**A SUSAR is defined as any untoward medical occurrence that, at any dose:**

- Is believed to be related to study treatment and is both unexpected (ie the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the MHRA, European Medicines Agency (EMA), EC (see [Appendix 7](#))

### Recording AE and SAE

#### AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF (ie the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study treatment and the event).
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

### Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during using the DAIDS grading table ([http://rsc.tech-res.com/docs/default-source/safety/daids\\_ae\\_grading\\_table\\_v2\\_nov2014.pdf](http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf)) and assign it to 1 of the following categories: Events):

- Grade 1, Mild: no or minimal interference with usual social & functional activities.
- Grade 2, Moderate: greater than minimal interference with usual social & functional activities.
- Grade 3, Severe: inability to perform usual social & functional activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- Grade 4, Life Threatening: inability to perform basic self-care functions
- Grade 5, Death

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

**Reporting of SAE to GSK****SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the Communication Plan.

**SAE Reporting to GSK via Paper CRF**

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by

telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Communication Plan.

## **12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information**

### **Definitions**

#### **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

#### **Women in the following categories are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

### **Contraception Guidance**

#### **Male participants**

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame

Refrain from donating sperm for duration of study and for 14 weeks after study completion or from last dose. **Female participants**

Female participants who are not of childbearing potential do not need to use any methods of contraception.

Female participants of childbearing potential are not eligible to participate in this study.

Female participants will not participate in egg donation from dosing, for the duration of the study and for at least 28 days after the last dose of study treatment.

**Table 5      Highly Effective Contraceptive Methods**

<p><b>Highly Effective Contraceptive Methods That Are User Dependent <sup>a</sup></b>  <i>Failure rate of &lt;1% per year when used consistently and correctly.</i></p>
<p>Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> <li>• oral</li> <li>• intravaginal</li> <li>• transdermal</li> </ul>
<p>Progestogen-only hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> <li>• injectable</li> </ul>
<p><b>Highly Effective Methods That Are User Independent</b></p>
<ul style="list-style-type: none"> <li>• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation</li> <li>• Intrauterine device (IUD)</li> <li>• Intrauterine hormone-releasing system (IUS)</li> <li>• bilateral tubal occlusion</li> </ul>
<p>Vasectomized partner</p> <p><i>(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)</i></p>
<p>Sexual abstinence</p> <p><i>(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)</i></p>

**NOTES:**

- a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.



**Pregnancy Testing**

- Urine pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the SureScreen Diagnostics test in accordance with instructions provided in its package insert at screening and admission to each study period

**Collection of Pregnancy Information****Male participants with partners who become pregnant**

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

**Female Participants who become pregnant**

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in [Appendix 4](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

## 12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

### Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
<b>ALT-absolute</b>	<p>ALT<math>\geq</math>3xULN</p> <p>If ALT<math>\geq</math>3xULN <b>AND</b> bilirubin<sup>1,2</sup> <math>\geq</math> 2xULN (&gt;35% direct bilirubin) or INR &gt;1.5, Report as an SAE.</p> <p>See additional Actions and Follow Up Assessments listed below</p>
Required Actions and Follow up Assessments	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study treatment</li> <li>• Report the event to GSK <b>within 24 hours</b></li> <li>• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE<sup>2</sup></li> <li>• Perform liver event follow up assessments</li> <li>• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> </ul> <p><b>MONITORING:</b></p> <p><b>If ALT<math>\geq</math>3xULN AND bilirubin <math>\geq</math> 2xULN or INR &gt;1.5</b></p> <ul style="list-style-type: none"> <li>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24 hrs</b></li> <li>• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>• A specialist or hepatology consultation is recommended</li> </ul> <p><b>If ALT<math>\geq</math>3xULN AND bilirubin &lt; 2xULN and INR <math>\leq</math>1.5:</b></p> <ul style="list-style-type: none"> <li>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</li> </ul>	<ul style="list-style-type: none"> <li>• Viral hepatitis serology<sup>3</sup></li> <li>• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend</li> <li>• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 2 days of last dose<sup>4</sup></li> <li>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>• Fractionate bilirubin, if total bilirubin<math>\geq</math>2xULN</li> <li>• Obtain complete blood count with differential to assess eosinophilia</li> <li>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</li> <li>• Record use of concomitant medications on the concomitant medications report form including paracetamol/acetaminophen, herbal remedies, other over the counter medications.</li> <li>• Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b>If ALT<math>\geq</math>3xULN AND bilirubin <math>\geq</math> 2xULN or INR &gt;1.5:</b></p>

Liver Chemistry Stopping Criteria	
<p>liver event follow up assessments within <b>24-72 hrs</b></p> <ul style="list-style-type: none"> <li>Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline</li> </ul>	<ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.</li> <li>Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. <b>NOTE: not required in China.</b></li> <li>Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.</li> </ul>

1. Serum bilirubin fractionation will be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT  $\geq$  3xULN and bilirubin  $\geq$  2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT  $\geq$  3xULN and bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

## References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et.al.. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

## **12.7. Appendix 7: Safety Reporting to Ethics Committee and Regulatory Authorities**

### **Events Requiring Expedited Reporting**

SUSARs are subject to expedited reporting to the MHRA, EMA and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of a study treatment or that would be sufficient to consider changes in the study treatments administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the participant has completed the clinical study where the sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the study treatments and likely to affect the safety of the participants, such as:
  - an SAE which could be associated with the study procedures and which could modify the conduct of the study
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - any anticipated end or temporary halt of a study for safety reasons and conducted with the same study treatments in another country by the same sponsor

### **Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

### **Expedited Reporting of Events**

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures will be followed.

#### **Fatal or life-threatening SUSARs**

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. This responsibility will be delegated to the pharmacovigilance provider, GSK/ViiV.

The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

Any additional relevant information will be sent within 8 days of the report.

### **Other SUSARs**

It is the responsibility of the sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility will be delegated to the pharmacovigilance provider, GSK/ViiV.

The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

Any additional relevant information will be sent within 8 days of the report.

### **Urgent Safety Measures**

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of participants enrolled in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study participants.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the EC.

### **Reporting of Urgent Safety Issues**

Quotient Sciences is required to inform the appropriate competent authorities and the EC within 3 calendar days of the urgent safety issue.

### **Serious Breaches**

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the participants of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

**12.8. Appendix 8: Protocol Amendment History**

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).